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ON THE TREATMENT OF LEUKÆMIA WITH BENZOL.

By Lewellys F. Barker, M. D., and James H. Gibbes, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital and University.)

Previous to von Korányi's[1] communication on the use of benzol in the treatment of leukæmia and other disorders of the blood-forming organs, the interest in this chemical was essentially industrial in nature. In medical literature it had been considered by Santesson[2] in 1897, and by Selling[3] in 1910, it having been called to the attention of these authors through toxic symptoms in people whose occupations exposed them to its action. Both Santesson and Selling followed their clinical observations by the experimental production of benzol poisoning in animals. These clinical and experimental investigations were originally far from the field of therapy, but in the light of a new interpretation, have been the means of discovering what may turn out to be an efficacious drug in the treatment of certain blood-diseases. Von Korányi attributes his decision to try benzol in leukæmia to Selling's work, and this naturally brings the observations of the latter author again into prominence, rendering a brief review of his findings desirable.

Three cases which were clinically classified as hæmorrhagic purpuras occurred in girls working in a canning factory near Baltimore. Their specific employment brought them into constant contact with the fumes of benzol which evaporated from a mixture used in soldering the tops on the cans. These young girls, each of them about fourteen years of age, entered the medical clinic of The Johns Hopkins Hospital with complaints of "spots on the body and giddy spells." Among their symptoms may be mentioned weakness, abdominal pain, and bleeding from the mucous membranes. Physical examination showed pallor, purpuric spots, and hæmorrhages in the retinæ. The blood-pictures were characterized by marked secondary anæmia and leucopænia, the white blood cells being as low as 140 per cmm. in one of the patients. The white blood count in this particular patient continued to fall after her admission to the hospital, *i. e.*, in spite of the fact that the exciting cause had been removed. This persistence of effect after benzol is withdrawn has been seen in its use in leukæmia, and is of considerable importance in determining at what point in the fall of the leucocytes its administration should be stopped. Cases in which the drug has been discontinued when the leucocytes had reached 12,000 to 14,000, have subsequently shown a normal count or even a leucopænia. Two of the patients reported by Selling died. Clinically, they had shown very extensive purpura and bleeding from the mucous membranes, and it is of particular interest to note that blood platelets were almost entirely

absent from one and reduced to 2500 per cmm. in the other. Duke's [4] recent suggestion that a deficiency of platelets is responsible for certain forms of hæmorrhagic disease is of interest in this connection. The differential counts revealed a relatively marked decrease in the polymorphonuclear cells, while the lymphocytes were relatively increased. At autopsy, the bone marrow was found to be aplastic, and a note was made that in one of the cases the spleen showed areas of hyaline necrosis affecting the Malpighian corpuscles. The other findings were incidental to the anæmia or had no apparent bearing upon the condition under investigation. The third patient presented symptoms entirely in accord with the other two, except that the gastro-intestinal manifestations seem to have been somewhat more prominent, as was evidenced by the anorexia and vomiting. Her anæmia was much less profound, the hæmoglobin being 54 per cent; the leucopænia was of a low grade (w. b. c. 4400), and her platelet count was 104,000 per cmm., this last corresponding with the fact that her purpuric eruption was not very extensive. Thus, Selling in his article described, as the clinical evidences of benzol poisoning, giddiness, headache, gastrointestinal symptoms, purpura, anæmia, and leucopænia. And these, as we shall see, are the danger signals that we should be on the lookout for, now that the chemical has become a therapeutic agent.

The experimental investigations which followed the appearance of these cases consisted in the subcutaneous injection of benzol into rabbits, in doses "suitable to produce chronic or subacute poisoning." A diminution in the white blood cells was the striking result obtained, while the red blood cells were much less readily affected. But after a prolonged exhibition of the drug a severe secondary anæmia was produced. Post mortem examination confirmed this somewhat selective action, the bone marrow disclosing a great diminution in the polymorphonuclear cells and degenerative changes in the myelocytes, the red blood cells remaining practically unaffected. This action of benzol in certain dosage, destroying white blood cells or inhibiting their formation in the leukopoietic fissures, without injury to the red cells or to the erythropoietic apparatus, was clearly before the profession in 1910, and it seems but a short step from this to the therapeutic use of benzol in leukæmia.

In connection with the poisonous action of benzol, a few instances of recorded intoxication may here, appropriately, be mentioned. Santesson's and Selling's cases have been referred to above. Schultze [5] reports an instance of three men who were poisoned while working with a machine from which they inhaled the fumes of benzol. One of the three died. Beisele [6] tells of a workman who was painting the inside of a vessel with a solution containing 10 per cent benzol when he was taken suddenly ill with pain in the head and vertigo, and shortly passed into a drunken-like stupor. He suffered for some time from memory disturbances, but gradually recovered. Finally Duke [7] employed benzol experimentally as a means of varying the platelet count in rabbits. He found that with doses sufficiently large to prove fatal in about eleven days, there was an initial rise in the number of platelets followed by a rapid fall, amounting almost to disappearance in some instances. This change was accompanied by a severe anæmia and leucopænia. In smaller doses, benzol acted as an irritant, there being a steady increase in the platelet count. This platelet destruction should be kept in mind as a possible explanation of the purpura and hæmorrhages from the mucous membranes that are seen in cases of benzol poisoning.

In July, 1912, von Korányi reported the first case of splenomyelogenous leukæmia in the treatment of which benzol was used. He states that he was led to the institution of this therapy through the pharmacological effects of the chemical as illustrated in Selling's experiments, *i. e.*, an inhibition of the white blood corpuscle-forming organs and a neutral effect or a stimulant action upon the production of red blood cells and hæmoglobin. A brief recital of von Korányi's case will serve to outline an apparently typical course under this mode of treatment. His patient was a woman, 32 years of age, who entered his clinic on the 30th of January, 1912, complaining of weakness and of enlargement of the abdomen. On examination, in addition to the pallor, the spleen was found to reach one hand's breadth below the umbilicus and to extend medialward, to the mid-line. There was tenderness over the sternum. At this time the blood examination showed: r. b. c., 3,100,000; w. b. c., 220,000; and the differential count revealed 16 per cent myelocytes. There was an exposure to X-rays on February 1. On February 6, the white blood cell count was 160,000. On February 16 it was 200,300, and on that date benzol was begun in doses of 3 gm. daily, the dosage being increased on March 1 to 4 gm. a day. The drug was continued in this quantity throughout its administration. The blood counts on subsequent dates were:

February 23,	white	blood	cells	= 173,000
March 1,	"	"	"	= 198,000
March 22,	"	"	"	= 120,000
April 4,	"	"	"	= 65,000
April 23,	"	"	"	= 19,600
May 12,	"	"	"	= 12,000
May 15,	"	"	"	= 8,000

The drug was then discontinued. At the beginning of the course the red blood cells fell to 3,000,000, while at the end they were found to be 4,000,000. The spleen was considerably reduced in size, and the patient's general condition was markedly improved. The last examination which is reported was made on July 1, approximately six weeks after treatment was stopped, and the number of white blood cells had not changed. From his experience with the drug, von Korányi formulates the following conclusions:

1. Benzol first tends to increase the white blood cells, but shortly leads to an improvement in the leukæmic condition. The fall in the white blood count usually begins at the end of the second week or at the beginning of the third week of therapy, the decrease at first being slow and then quite rapid. The general condition of the patient is improved just as with X-rays and other forms of treatment.

2. Benzol acts more slowly than X-rays but some patients improve under its administration who do not respond to the usual therapy. Previous or concomitant applications of the X-ray seem to hasten the action of the new drug.

3. The drug can be safely given in doses of 4 gm. daily, and its administration with equal parts of olive oil seems to lessen the tendency to produce unpleasant symptoms, such as heart-burn, eructations, and vertigo.

4. Benzol seems to be efficacious in the treatment of polycythemia with splenic enlargement, one case showing a fall in red blood cells from 9,000,000 to 6,700,000 after three weeks of treatment.

The rapid accumulation of new data on this subject has tended to confirm, in almost every detail, von Korányi's original statements. There are some instances in which the transient increase in the leucocytes does not take place, but the evidence to date seems to indicate that this rise is the rule and that its failure to appear represents the exception. Shortly after von Korányi's report, Királyfi [8] published from the same clinic eight cases in which benzol had been used. In some, the dosage had been increased to 5 gm. daily without untoward effects, and we have used, in the case we are about to report, the drug in this quantity over a long period with no unpleasant manifestations. Királyfi's cases were grouped as follows: Five cases of splenomyelogenous leukæmia, one case of lymphatic leukæmia, one case of pseudo leukæmia, and one case of polycythæmia. One of the splenomyelogenous cases left the hospital prematurely with a leucocyte count of about 100,000, but the others of this type showed improvement in their general condition and a fall of their white blood cells to normal. The patient with lymphatic leukæmia likewise showed a marked reduction in the total leucocyte count, from 140,000 to 8000, but the differential count still showed 63 per cent of lymphocytes at the end of the treatment. The patient with pseudoleukæmia had a leucocyte count of 24,100, the formula being normal. The glandular enlargements were successfully diminished by the aid of arsenic and X-rays. However, the count of the white blood cells still remained high. For this reason, benzol was given, and in about six weeks the count had been reduced to 12,000. The polycythæmia was decreased from approximately 9,000,000 to 6,000,000 under the influence of the drug. The patient then left the hospital; when seen a short time later the number of his red cells had again increased.

Billings,[9] of Chicago, has recently reported five cases in which he used benzol, four of his patients suffered from myelogenous leukæmia, one of them from lymphatic leukæmia. This last author notes essentially the same changes as reported by von Korányi, but draws attention to the entire disappearance of myelocytes from the blood in one of his patients, whose white count had been reduced from 191,000 to 3600. The percentage of myelocytes has been uniformly less after the total cell count has decreased—as one would expect from similar experiences with arsenic. But it is decidedly unusual for the myelocytes wholly to disappear from the peripheral blood. It might be interesting to speculate as to the significance of this finding; does it represent a return of the bone-marrow function to normal or are we dealing simply with a temporary paresis of its activity? Billings' patient with lymphatic leukæmia behaved similarly to Királyfi's in that the total leucocyte count reached normal while the percentage of mononuclear cells remained high.

Gouget [10] presents a most satisfactory review of the literature on this subject, having collected six cases in addition to those reported by von Korányi and Királyfi. He tabulates these cases, indicating the fall of leucocytes under treatment, as follows:

Kovacs [11]	.....	white cells	fell	from	350,000 to 12,000
Stern [12]	.....	"	"	"	264,000 to 12,000
Tedesko [13]	.....	"	"	"	120,000 to 11,000
Eppinger [14]	.....	"	"	"	300,000 to 7,000
Stein [15]	.....	"	"	"	225,000 to 6,000
Wachtel [16]	.....	"	"	"	182,000 to 13,000

Tedesko's patient was a woman, 53 years old, suffering from lymphatic leukæmia, the blood showing on admission 84 per cent of small mononuclear elements. Under treatment, the leucocyte count fell to 11,000, the percentage of mononuclears remaining practically unchanged, while the red blood cells underwent a remarkable increase—from 975,000 to 3,770,000. It is noteworthy that the failure of benzol materially to change the differential blood formula in this case of lymphatic leukæmia is in keeping with the findings of other authors. On the other hand, the percentage of myelocytes has been considerably reduced along with the fall in the total leucocyte count, in every case of myelogenous leukæmia treated by this method.

We thus have from the literature reports of eighteen cases in which benzol has been used. These eighteen patients represent the following conditions:

Splenomyelogenous leukæmia	13 cases
Lymphatic leukæmia	3 "
"Pseudo leukæmia"	1 case
Polycythemia with splenic tumor	1 "

We, ourselves, desire now to add a case of splenomyelogenous leukæmia that responded in the usual manner to benzol therapy. A white male, 57 years old, referred to one of us by Dr. Randolph, of Charlottesville, Va., entered the medical service of The Johns Hopkins Hospital on November 23, 1912, complaining of nervousness, insomnia, and general psychasthenic symptoms. On a previous admission, May, 1906, he had presented similar complaints, his condition at that time having been diagnosed as neurasthenia. The blood count, in this earlier history, revealed: red blood cells 5,200,000, white blood cells 6500. He was in exceptionally good health after leaving the hospital in 1906 until the onset of the symptoms which led to his present admission. The *family history* is unimportant. In his *past history,* the positive points are: malarial fever at 15 years of age; four gonorrhœal infections about 20 years ago with a resulting chronic prostatitis, a chancre 19 years ago for which he was treated and "pronounced cured," and a marked history of alcoholism and tabagism. The symptoms which he considers as due to the *present illness* began approximately two months before his entrance to the hospital. They consisted of extreme nervousness, anorexia, insomnia and marked depression with feelings of general inefficiency.

The *physical examination* was entirely negative. The spleen was not palpable on admission, has not been felt at any time since, and the splenic dullness was not increased. There was no general glandular enlargement.

On November 24, 1912, the blood picture showed:

Red blood cells	3,672,000
White blood cells	345,000
Hæmoglobin (Sahli)	65%

Differential count with Ehrlich's stain made by Dr. Sidney R. Miller gave the following formula:

	Cells counted.	Percentage.
Polymorphonuclear neutrophiles	387	60.75%
Polymorphonuclear eosinophiles	5	0.75%
Polymorphonuclear basophiles	12	1.99%
Small mononuclears	35	5.48%
Large mononuclears	17	2.65%
Transitionals	14	2.19%
Neutrophilic myelocytes	158	24.79%
Eosinophilic myelocytes	3	0.47%
Basophilic myelocytes	4	0.62%
Myeloblasts	2	0.31%
	637	100.00%

In making the count, 8 normoblasts were seen and 1 megaloblast.

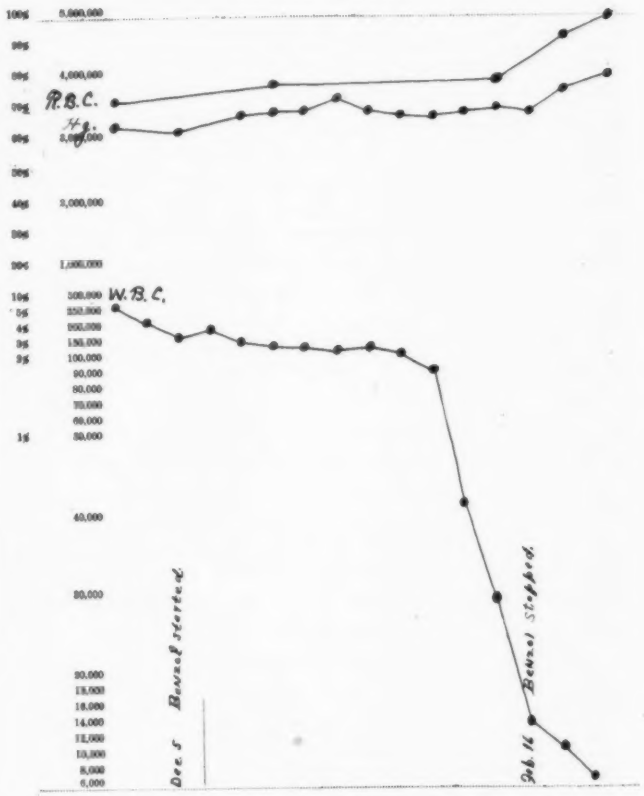
The *Wassermann reaction* was *positive* on November 30, 1912.

X-rays of long bones were negative on November 29, 1912.

The *urine* presented fairly constant findings throughout. Quantity, 1800 to 2000 cc. for 24 hours; specific gravity, 1018 to 1020; reaction, acid; a granular sediment; hyaline and granular casts and large numbers of uric acid crystals were seen on microscopic examination. Dr. Guthrie made an especial examination of the urine for Bence-Jones body and found it present. In a recent paper Boggs and Guthrie" mention three cases of lymphatic leukæmia from the literature which showed a Bence-Jones proteinuria, while nine cases of lymphatic leukæmia and fourteen of myelogenous leukæmia are listed in which this condition was absent. As far as is known to us, our case is the only one of this variety of leukæmia in which the urine has contained the Bence-Jones body.

Treatment and Course.—From November 24 to November 26, the patient received no treatment other than absolute rest in bed. On the latter date, Fowler's solution was begun in doses of 3 minims three times a day, increasing one minim per dose each day. This treatment was discontinued on December 5. On November 29, X-ray pictures were taken of the tibia and fibula of one leg, this being the single exposure to X-rays. On December 4, on account of the positive Wassermann an intravenous injection of 0.3 gm. of neosalvarsan was given. On December 5, the white blood cells were 191,000, and on this day the benzol treatment was started; 2 gm. were given the first day, and the dose was increased 1 gm. each day until it reached 5 gm. The drug was then continued in this quantity until withdrawn on February 15, 1913. Five days after this treatment was started the white blood cells rose to 210,000. They then began to fall, reaching 188,000 on December 16, and continued to fall slowly until January 9, when the reduction became much more rapid. This was almost six weeks after the beginning of the treatment. In another six weeks, the white blood count had fallen to 10,200. For fear of causing too marked a hypoplasia of the marrow, the drug was discontinued at this point, and one week later the leucocyte count was 7800. During the period of treatment the red blood cells had increased from 3,600,000 to 5,000,000 and the hæmoglobin reached 82 per cent.

BLOOD CHART.



Top line = red blood cells.
Middle line = hæmoglobin.
Bottom line = white blood cells.

The drug was given in "5 grain" gelatin capsules, containing one-half gram each of chemically pure benzol and olive oil.

Another differential count with Ehrlich's stain was made by Dr. Sydney Miller on February 20:

	Cells counted.	Percentage.
Polymorphonuclear neutrophiles	440	88.0%
Polymorphonuclear eosinophiles	5	1.0%
Polymorphonuclear basophiles	3	0.6%
Small mononuclears	10	2.0%
Large mononuclears	16	3.2%
Transitionals	22	4.4%
Myelocytes	4	0.8%
	500	100.0%

It was noted that there was practically a complete absence of platelets during this count. The great reduction in the platelet count is of particular interest when viewed in connection with the occurrence of a purpura in the patient. This was first noticed as a small subcutaneous hæmorrhage on the back of one of his hands. By the end of the tenth week of treatment he had a rather extensive eruption over the lateral aspects of the legs and a few spots were visible scattered over the trunk. There was absolutely no increase in the condition after this time, in fact the purpura had cleared to some extent when the patient was discharged. On February 25, the day before discharge from the hospital, the bleeding-time was found to be only one and a half to two minutes. There was no bleeding from the gums at any time, and no epistaxis. The retinæ were perfectly clear when the patient left the hospital.

The *clinical notes* on the patient's condition show him to have made a steady improvement from the beginning of his treatment to the time of his discharge. The most marked subjective feature throughout was his extreme psychoneurotic state, but this became progressively better with the lowering of his white blood count. At no time during the administration of benzol did he complain of vertigo or eructations, nor was he troubled with colds or bronchitis. He did have a slight sensation of burning along the œsophagus at times, and the odor of benzol was perceptible in his breath.

Our case, as will have been seen, is in accord with previous reports, and so demands but little especial comment. The course of benzol administration extended over approximately eleven weeks, during which period the total number of white blood cells returned to normal, the red blood cells increased from 3,600,000 to 5,000,000, the hæmoglobin changed from 65 per cent to 82 per cent, and the patient's general condition showed definite improvement. In as far as we can judge of this new line of therapy in leukæmia from the observation of the patient reported, we share the belief of most authors as to its efficacy in reducing the white blood cells, and in leading to an associated subjective improvement of the patients. Our patient progressed in a satisfactory manner with the exhibition of benzol alone, but we feel that the possible value of other accessory measures, such as X-rays, arsenic, thorium X, and radium, in the therapy of leukæmia should be kept in mind. Pappenheim's [15] recent criticism of the benzol treatment, based upon a theoretical consideration of Selling's work and an attempt to apply some experimental studies made by himself to clinical medicine, has been replied to by von Korányi.[16] The latter author holds that the production of definitely noxious manifestations in rabbits and anatomical lesions of the kidneys, liver, lungs, and spleen, by relatively immense doses of benzol, does not necessarily imply that similar effects follow upon the use of the drug as it is now therapeutically employed in leukæmia. Von Korányi incidentally mentions that one of his patients is, at the present time, apparently well, ten months after the discontinuation of treatment. Tedesko [20] likewise replies to Pappenheim, stating that he has observed no bad results clinically, and warning against such criticisms as tending to prevent an adequate testing of the new drug. The ultimate place of benzol in the treatment of leukæmia, polycythæmia, and Hodgkin's disease can be determined only through further studies which include careful clinical observations.

Finally, we wish to emphasize the facts, first, that benzol does possess dangerous toxic properties; second, that its clinical effects are not yet clearly understood, and, third, that the greatest care should be exercised in its administration. A studious regard for the dosage as thus far determined, a watchfulness for the manifestations of poisoning that are well defined and easily detected, and a willingness to employ other measures in conjunction with this drug, are means that will serve to give the new treatment a fair trial and prevent its falling into an undeserved disrepute. Certainly, no patient should be treated by benzol unless he can be kept under continuous close observation; for the present, therefore, it may be well to restrict its use to the treatment of patients in hospitals, rather than to run the risks attendant upon its extension to domiciliary practice.

Addendum.—On April 9, 1913, approximately seven weeks after the benzol treatment was discontinued, the patient returned to the hospital for salvarsan. He had received no medication in the interim. His blood count at this time showed:

Red blood cells	4,096,000
White blood cells	6,800
Hæmoglobin (Sahli)	76%

Differential count (Wilson's stain):

	No. cells.	Percentage.
Polymorphonuclear neutrophiles	147	73.5%
Polymorphonuclear eosinophiles	2	1.0%
Polymorphonuclear basophiles	2	1.0%
Small mononuclears	7	3.5%
Large mononuclears	4	2.0%
Lymphocytes	25	12.5%
Transitionals	5	2.5%
Myelocytes, neutrophiles	6	3.0%
Myelocytes, basophiles	2	1.0%
	200	100 %

He was given 4.5 gm. of neosalvarsan intravenously and iron in the form of Blaud's pills. When discharged on April 26, his blood count was:

Red blood cells	4,800,000
White blood cells	7,000
Hæmoglobin (Sahli)	79%

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BENCE-JONES PROTEINURIA IN LEUKÆMIA: A REPORT OF FOUR CASES: THE EFFECT OF BENZOL ON THE EXCRETION OF THE PROTEIN.

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(From the Clinical Laboratory of The Johns Hopkins Hospital and University.)

The occurrence of Bence-Jones proteinuria in multiple myeloma is well known. That it may occur in conditions other than myelomatosis has also been pointed out by various observers and the writers have recently reviewed the literature on this particular aspect of the subject.[1] Leukæmia is one of the diseases with which the excretion of this unusual protein may be associated, but the phenomenon has been noted in only four instances, and only in the chronic lymphatic form of the disease, although many cases of all the various types have been repeatedly examined. In a series of fourteen leukæmic patients (acute lymphatic, 2; chronic lymphatic, 4; acute myeloid, 3; chronic myeloid, 5) which has recently been carefully studied, the Bence-Jones body has been found in the urine in four instances (chronic lymphatic, 1; chronic myeloid, 3). Since this is the first observation of Bence-Jones proteinuria in chronic myeloid leukæmia and also as it has been so rarely observed in any form of the disease, it has seemed advisable to report the cases in some detail, especially since these cases seem to furnish additional evidence in support of the belief that a causal relationship exists between pathological changes in the bone marrow and the excretion of this protein.

Case I.*—The patient, aet. 57, male, white, a clerk, was admitted November 23, 1912, and discharged February 25, 1913.

Diagnosis.—Chronic myeloid leukæmia. There was a previous admission in May, 1906, for neurasthenia, when the blood count was normal.

Past History.—Malaria 42 years ago. Lues 20 years ago. Fairly constant drinker. Several attacks of gonorrhœa in past 20 years, with resulting chronic prostatitis.

Present illness.—Began the last of September, 1912, when he had a nervous shock, since which time he has felt run down and has lost 7 pounds in weight. There was anorexia, insomnia and depression, with physical weakness, indigestion, constipation and nycturia.

Physical Examination.—Patient was well nourished. Pupillary reactions normal. No enlargement of thyroid or cervical lymphatic glands. Thorax well formed. Heart and lungs normal. Abdomen apparently normal. Liver and spleen not enlarged. Stools normal.

Blood Examination.—R. B. C., 3,672,000; W. B. C., 345,000; Hb., 65%; Color index, 0.89; Differential leucocyte count:

Polymorphonuclear neutrophiles	60.75%
Polymorphonuclear eosinophiles	0.75%
Polymorphonuclear basophiles	1.99%
Small mononuclears	5.48%
Large mononuclears	2.65%
Transitionals	2.19%
Myelocytes, neutrophilic	24.79%
Myelocytes, eosinophilic	0.47%
Myelocytes, basophilic	0.62%
Myeloblasts	0.31%

Nucleated R. B. C.—8 normoblasts and 1 megaloblast seen in counting 637 W. B. C.

Wassermann reaction positive. Salvarsan 0.3 gm., intravenously on December 4. Reaction at time of discharge still positive. The X-ray examination revealed no abnormality in the long bones.

Benzol Therapy.—Started December 5, 2 gm. benzol per diem in four doses by mouth, increasing by 1 gm. daily until 5 gm. was reached and continued at this dosage. After four weeks of benzol treatment the W. B. C. count had fallen to 166,000. In the 7th week the W. B. C. count was 96,000; 8th week, 42,000; 9th week, 28,000; 10th week, 14,000; 12th week, 7,800. At this time, when he was discharged, the blood examination showed: R. B. C., 5,000,000; Hb., 82%; Color index, 0.8; Differential W. B. C. count:

Polymorphonuclear neutrophiles	88.0%
Polymorphonuclear eosinophiles	1.0%
Polymorphonuclear basophiles	0.6%
Small mononuclears	2.0%
Large mononuclears	3.2%
Transitionals	4.4%
Myelocytes	0.8%

No nucleated R. B. C. seen. Platelets practically absent. The patient's subjective and objective symptoms seemed to be greatly improved. He is to return for observation.

Characteristics of the urine.—Total amount, 1650 cc.; clear, amber; acid; sp. gr., 1018; heavy, yellow, granular sediment with coarse uric acid crystals; no sugar; protein present, too small in amount for Tsuchiya estimation; total chlorides, 10 gm. Microscopically:—numerous uric acid crystals; many clumps of amorphous urates; many finely and coarsely granular casts; a few epithelial cells; no R. B. C. or W. B. C.; occult blood test (guaiac), negative.

Functional renal tests were reported by Dr. W. A. Baetjer as follows: Phenolsulphonephthalein output, 27% in first hour; 28% in second hour; or 55% in two hours (slightly below normal).

* This case is reported from the clinical and therapeutic standpoint by Drs. Barker and Gibbes in this issue of the Johns Hopkins Hospital Bulletin.

Lactose, six hours required for excretion (slightly delayed). KI normal; total excretion in less than 48 hours. Rest nitrogen (blood serum), 0.42 gm. per litre (normal). Sodium chloride-excess normally excreted; excreting 8-10 gm. daily on constant diet; increase of 7 gm. given; this excess was excreted by increased concentration in the urine without increase in fluid output. *Conclusion:* Slight impairment of renal function of vascular rather than tubular origin, as indicated by the slight delay in lactose excretion (Schlayer), while the tubular tests, NaCl and KI gave normal results.

Protein Tests.—The filtered urine gave no precipitate with acetic acid in the cold, nor when dropped into a beaker of distilled water, showing the absence of mucin, nucleoalbumin and globulin. The unacidified urine gave no precipitate when heated to 60° C. When the urine, slightly acidulated with dilute acetic acid (5%) was heated slowly, precipitation began at 51° C. and was apparently complete at 60° C., the urine being turbid and the precipitate settling out in flocculi on standing. This precipitate was almost completely soluble on boiling, but reappeared when cooled, dissolving again on boiling. A fresh, acidulated specimen, heated to 60° C. for one hour and then cooled, showed a precipitate as above, the filtrate from which remained clear on reheating to 60° C. for one hour and cooling; showing the complete removal of the protein precipitable at this temperature. The same specimen, heated slowly from 60° to 90° C. and eventually boiled, gave no further precipitation either immediately or on cooling. Spiegler and biuret tests applied to this specimen were also negative, demonstrating the absence of serum albumin. The layer test with concentrated nitric acid in the cold gave a sharp white ring at the line of junction. With a few drops of dilute nitric acid (25%) in the cold, a turbidity was produced which almost completely disappeared on boiling and reappeared on cooling. With two volumes of saturated ammonium sulphate solution there was a flocculent precipitate, the filtrate from which did not give a biuret reaction, while the precipitate was readily soluble in water, from which it could be reprecipitated on further addition of two volumes of saturated ammonium sulphate solution. For the further study of the precipitate obtained by heat, the urine for two days (3-4 litres) was filtered through plain paper to remove the sediment, the clear filtrate slightly acidified with acetic acid and heated to 60° C., in a water bath over night. The resulting dark brown, flocculent precipitate was collected by decantation and washed repeatedly with distilled water; it was then centrifugalized to a small volume, suspended in 20 cc. of water and a few drops of 5% sodium carbonate solution added, when on heating to 45° C. the precipitate was completely dissolved, yielding a clear, dark brown solution. This was dialyzed in a collodion sac against running water for 24 hours. The clear, slightly brownish solution was neutral to litmus; gave no precipitate on boiling; became slightly cloudy on the addition of dilute acetic acid in the cold; and on warming this acidified fluid there was complete precipitation at 60° C., and partial resolution on boiling. The addition of a few drops of calcium chloride solution to the acidulated dialyzate intensified the sharpness of the reaction, so that solution was complete at the boiling point with precipitation on cooling. Another portion of the dialyzate acidified with dilute nitric acid (25%) yielded similar results.

The total urine of two other days (3 litres) was treated with ammonium sulphate to two-thirds saturation and the brownish-yellow precipitate collected by decantation. The supernatant fluid was filtered and tested by heat and acetic acid, nitric acid in the cold, Spiegler and biuret, and found free from protein. The ammonium sulphate precipitate was redissolved in water and again precipitated by two-thirds saturation with ammonium sulphate, this process being repeated three times. The final precipitate was dissolved in water, placed in a thin collodion sac and dialyzed against running water for 24 hours. Another portion of the precipitate was dialyzed in a similar manner against distilled water for 72 hours. At the end of this time, the water outside the sac was found free from protein by the Spiegler and biuret tests, showing that none of the protein passed through the sac. The portion dialyzed against running water, when faintly acidified with 5% acetic acid, gave a slight turbidity in the cold, a flocculent precipitate at 60° C. and partial solution on boiling, which became complete on the addition of a few drops of calcium chloride solution.

The further course of this patient under treatment is of considerable interest as furnishing experimental evidence of the relation of the bone marrow or blood forming centres to the excretion of the Bence-Jones body. The urine was followed in repeated and careful examinations over a period of about twelve weeks. The findings were practically constant until the benzol treatment was begun. There was a moderate polyuria, the urine being of normal specific gravity, acid in reaction, with heavy precipitate of urates and uric acid. No sugar was present and no protein other than the Bence-Jones, and this in small amounts. Microscopically there were a few finely and coarsely granular casts. The total chlorides were followed for a week, showing an output which varied from 9.6 gm. to 15.2 gm., with an average of 11.6 gm. per diem. With the development of the effect of the benzol treatment on the blood picture, there was concurrent diminution in the excretion of the Bence-Jones protein, until during the last few days of observation it was no longer demonstrable. It is especially to be remarked that with the disappearance of the Bence-Jones body, there was no evidence of any other type of protein excretion, the urine remaining free from albumin, nor was any true albumose (proteose) detected by the Salkowski method either at this time or during the period before the benzol treatment was begun. During the benzol period the urine became gradually more concentrated, dropping to one-half the original volume, darker in color, more strongly acid, and very rich in uric acid and urates, which began to precipitate immediately after voiding, giving the urine a milky appearance. At no time was there any spontaneous precipitation of the Bence-Jones protein, not even in specimens kept for several months over chloroform.

In connection with the foregoing, detailed study, we should like to note briefly a second case, in which we were able to make only one examination of the urine, as the patient, who came from a long distance for diagnosis, was in the hospital only one night.

CASE II.—The patient, a white man, aet. 33, married, a carpenter, was admitted January 16, 1913, and discharged January 17, 1913.

Diagnosis.—Chronic myeloid leukæmia.

Complaint.—Enlarged spleen and weakness.

Family History.—Unimportant.

Past History.—No serious illness in childhood or at any time until the present.

Present Illness.—Began about fifteen months before admission with anorexia, indigestion and pain in the epigastrium, lasting about three months. After the subsidence of these symptoms the patient noticed a lump in the left side which increased steadily in size for five or six months, at which time there developed a severe pain over the region of the mass. This lasted about three weeks and necessitated the patient's sitting up constantly in a chair. At this time the mass almost filled the abdomen and extended into both flanks, but has since become smaller. There was oedema of the legs and fulness in the abdomen which has diminished in the last five months. Transient attacks of pain have recurred from time to time.

Physical Examination.—The patient was well nourished; color slightly yellowish; pupils and eye movements normal; slight

general glandular enlargement. Lungs normal. Heart normal. Abdomen very prominent, especially over the left half which was filled by a large firm spleen, extending 20 cm. below the ensiform cartilage in the midline and 25 cm. in transverse diameter. The liver was not appreciably enlarged. No ascites. The superficial abdominal veins were somewhat distended. Blood pressure normal.

Blood Examination.—R. B. C., 3,072,000; W. B. C., 506,000; Hb., 50%; Color index, 0.83; Differential leucocyte count:

Polymorphonuclear neutrophiles	50.3%
Polymorphonuclear eosinophiles	4.6%
Polymorphonuclear basophiles	0.3%
Small mononuclears	5.6%
Large mononuclears	6.6%
Transitionals	3.3%
Myelocytes, neutrophilic	27.3%
Myelocytes, eosinophilic	3.2%
Myelocytes, basophilic	0.6%

Nucleated R. B. C. 2 normoblasts seen in counting 500 white cells.

Urinary Examination.—The single specimen of urine examined was yellow, slightly turbid, acid in reaction, sp. gr. 1014. No sugar. Small amount of protein present. Microscopically: flocculent sediment showing a few epithelial cells and granular casts. The acetone, occult blood and diazo tests were negative. On more detailed examination of the protein it was found that there was no globulin or serum albumin present. With dilute acetic acid in the cold, a precipitate was obtained which yielded, after hydrolysis, qualitative tests for a reducing body and for sulphuric acid and was apparently the so-called Mörner's body. After complete removal of this body, further tests were carried on as follows: The remaining urine gave a characteristic precipitate at 60° C. with partial resolution on boiling and reprecipitation on cooling. The filtrate from this reaction did not give a further precipitate on heating to 60° C. nor at the boiling point. The precipitate was readily soluble in dilute sodium carbonate solution on gentle warming at a low temperature and gave the reactions for Bence-Jones protein in alkaline solution. With dilute nitric acid (25%) there was an initial turbidity in the cold, increased on warming, partial clearing on boiling, and reprecipitation on cooling. The addition of two volumes of saturated ammonium sulphate solution gave a flocculent precipitate, soluble in water and on dialysis. It seems evident, therefore, that this urine contained Bence-Jones protein and Mörner's body.

Case III.—The patient, a colored man, aet. 60, married, a laborer, was admitted July 2, 1913, and at the time of writing, August 12, 1913, is still in the hospital.

Diagnosis.—Chronic myeloid leukæmia.

Complaint.—Swelling of legs, shortness of breath, and occasional choking sensation in throat.

Family History.—Unimportant.

Past History.—Gonorrhœa at 26; winter cough for several years. Hæmorrhoids which have bled occasionally at intervals of six to twelve months during past fifteen years. Nycturia for three years. Loss of fifteen pounds in weight.

Present Illness.—Health good until seven months before admission, when he began to have dyspnœa on exertion and swelling of the ankles at night. This condition cleared up on resting, but returned when he went back to work. As a result, he has suffered intermittently until three weeks ago, when he stopped work. The dyspnœa and œdema increased up to one month ago, when the patient began to have orthopnœa as well. For the past four months he has had morning cough, with yellowish, blood-tinged expectoration, and for the last two months, night sweats once or twice weekly. Giddiness for three months. Diarrhœa for four days prior to admission.

Physical Examination.—Some emaciation. Pallor of lips and mucous membranes. Fulness of superficial veins of arms, also of the veins of the lateral thoracic, umbilical and hypogastric regions. Arcus senilis. Pupillary reactions normal. Pyorrhœa and dental caries. Rather spongy gums. Slight general glandular enlargement.

Lungs.—Slight impairment at left apex and at bases behind, otherwise hyper-resonant throughout. Moist râles heard over both lungs.

Heart.—Somewhat enlarged; marked arhythmia; many extra systoles; slight systolic blow at apex, transmitted outward. Very marked sclerosis of peripheral arteries.

Abdomen.—Liver 6½ cm. below right costal margin, firm. Some shifting dulness in flanks. Oedema of both legs. Knee kicks not obtained. Plantar response normal.

Blood Examination.—July 15, 1913, R. B. C., 3,320,000; W. B. C., 336,000; Hb., 49% (Sahli); Color index, 0.73; Differential leucocyte count:

Polymorphonuclear neutrophiles	53.6%
Polymorphonuclear eosinophiles	4.4%
Polymorphonuclear basophiles	0. %
Small mononuclears	3.2%
Large mononuclears	0.8%
Transitionals	0.4%
Myelocytes, neutrophilic	36.4%
Myelocytes, eosinophilic	1.2%

Nucleated R. B. C., both normoblasts and intermediates seen.

Wassermann reaction negative.

Blood Pressure.—140 mm. Hg. (Tycos).

Temperature.—Gradually rose in first four days to 102° F. and then gradually fell to normal with an occasional slight elevation, but on July 23d it rose to 100.6° F. and on the 24th reached 103° F. Gradual fall since then.

Pulse.—Irregular, but relatively lower than temperature throughout.

Treatment.—Rest in bed; "cardiac diet"; fluid intake limited to 1500 cc.; course of twelve doses of tincture of digitalis; 1 cc. four times daily, begun July 4th; benzol with olive oil in one gm. doses by mouth, begun twice a day on July 29 and gradually increased until five doses were given daily. Under the benzol therapy the white blood cells fell to 230,400 on August 2 but two days later, had risen to 294,000. On August 7 the count was 202,000 and on the 10th, 210,000.

Urine.—Total specimens of the patient's urine were examined for fifteen consecutive days before the benzol treatment was begun, during which time the following characteristics were noted.

Color.—Yellow to orange, often cloudy.

Amount.—In twenty-four hours, 315 to 1475 cc., gradually increasing in volume; average 950 cc.

Specific Gravity.—1008 to 1011; average 1009.

Reaction.—Acid.

Sugar.—Absent.

Protein.—Present.

Total Chlorides.—4 gm.

Urobilin.—Present.

Indican.—Present.

Microscopically.—Hyaline and granular casts; cylindroids; mucous shreds; epithelial cells; urates and uric acid crystals.

Occult Blood Test.—Negative.

Application of the same tests to establish the nature of the protein, as used in Cases I and II, showed that minute traces of serum albumin were excreted on seven occasions, but could not be detected at the other examinations, while Mörner's body and the Bence-Jones protein were constantly present. Although all three types of protein were too small in amount for ordinary quantitative estimation by the Tsuchiya method, judging from the intensity of the reactions and the amounts of pre-

cipitate obtained, serum albumin, when present, was least in amount, Mörner's body next, and the Bence-Jones protein relatively more abundant. No albumose (proteose) was found by the Salkowski method and globulin was absent throughout.

After benzol was started on July 29 the urine was followed carefully over a period of two weeks, during which time no material changes were noted. The three proteins found before were still present in small, but variable amounts and no others were detected. The persistence of the Bence-Jones body after two weeks of benzol therapy was not considered surprising as the white blood count was still over 200,000.

CASE IV.—The patient, a white man, married, a lumberman, was admitted June 12, 1913, and discharged July 5, 1913.

Diagnosis.—Chronic lymphatic leukæmia.

Complaint.—Swelling of glands of body.

Family History.—Unimportant.

Past History.—Had the ordinary diseases of childhood. At 22 had measles followed by a pulmonary complication, chiefly involving the left side. During the following two years he was unable to work and had constant cough with some expectoration, fever and night sweats. At the end of two years he went back to work in the woods and has been able to continue at his occupation since then. Sever attack of bronchitis four years ago. Morning cough for last two to four years with white expectoration; none during the day. Piles for ten to fifteen years, bleeding occasionally, more freely and frequently during the past year. Denies venereal infection. His wife has had one miscarriage at two months. One child living and well. Patient drank whiskey daily for fifteen years, then to excess for five years, but has taken none during the past four years.

Present Illness.—Sixteen months before admission the patient had an attack of tonsillitis and quinsy, after which his tonsils remained large. In February, 1913, his tonsils still further increased in size but were not sore or tender. In March, 1913, he noticed enlarged glands at angles of his jaw, which have gradually grown in size. In May, 1913, his tonsils were removed. About June 1 he noticed enlarged glands in the axillæ and later in the groins. None of the glands have been painful or tender and at no time have they caused him any inconvenience. One week before admission he noted a swelling in the lower right axilla and a few days later purplish spots appeared over the right lumbar region.

Physical Examination.—Emaciation. Pallor of lips and mucous membranes. Slight jaundice. Purpuric spots over right axillary and lumbar region. Evidence of subcutaneous hæmorrhage in lower right axillary region. Very marked general glandular enlargement, the individual glands being discrete, movable, firm, and not tender. Striking hyperplasia of lymphatic tissue in pharynx and at site of tonsillectomy. Anisocoria, but normal pupillary response.

Lungs.—Signs of consolidation at left apex with moist râles throughout entire left side.

Heart.—Wide area of dulness behind the manubrium. Systolic murmur at apex, transmitted to axilla.

Abdomen.—Liver extended 6 cm. below the costal margin in the right mammillary line.

Spleen.—5 cm. below left costal margin, firm and nodular. Knee kicks present. Plantar response normal.

Blood Examination.—June 12, 1913, R. B. C., 2,880,000; W. B. C., 100,500; Hb., 55%; Color index, 0.96; Differential leucocyte count:

Polymorphonuclear neutrophiles	5.2%
Polymorphonuclear eosinophiles	0.4%
Polymorphonuclear basophiles	0.0%
Small mononuclears	88.0%
Large mononuclears	6.0%
Transitionals	0.4%

The *Wassermann* reaction was negative on June 13, but showed partial fixation (10-15%).

Tuberculin tests reported June 18: Calmette 1% and 5% negative; von Pirquet positive.

X-ray Examination of chest, June 14: Infiltration of both lungs; tuberculous consolidation of left apex.

Temperature.—During first week rose from normal in morning to 100° F. in p. m. Gradually the afternoon temperature fell to 99° F.

Pulse.—Relative tachycardia, most marked during first week, when it rose irregularly to 120, then gradually lower, but still in neighborhood of 100 on discharge.

Treatment.—Intravenous injection of *salvarsan* on June 14; *benzol*, one gm. with olive oil, in capsules by mouth; begun twice a day on June 13 and gradually increased until the patient was receiving five doses daily. Benzol discontinued on July 2. *X-ray* treatment three times weekly, beginning June 23. Tonics and additional feeding with eggs and cream.

During the patient's stay in the hospital his white blood count fell from 100,500 on admission to 55,000 one week later; then to 46,000 on June 24, and on July 1, four days before discharge, it had dropped to 17,600, while the red blood cells and hæmoglobin remained at practically the same level throughout the period of observation. There was marked improvement in the patient's general condition and the glands, especially those about the angles of the jaw, decreased appreciably in size and became softer in consistence.

Urinary Examination.—After the patient had been treated with benzol for two weeks his urine was submitted to special examination in this laboratory over a period of nine days with the following results. The urine was, as a rule, clear, and dark amber in color, becoming quite dark on standing. The amount for twenty-four hours was in the neighborhood of 500 cc. and the specific gravity varied between 1024 and 1035, the average being about 1028. The reaction was acid. Sugar was absent and protein present. The occult blood test (guaiac) was negative.

Total Chlorides.—6 to 7 gm.

Microscopically there were seen numerous cylindroids, a few hyaline and coarsely granular casts, epithelial cells, mucous shreds and uric acid crystals. For the identification of the protein, all of the tests used in Cases I and II were applied, as a result of which two general conclusions were drawn: (1) that there was no mucin, Mörner's body, albumose (proteose), globulin, or serum albumin present, and (2) that the protein present was the Bence-Jones body, as it responded characteristically to all of the tests. It was found in small, but readily appreciable amounts on the first five examinations, diminishing in quantity perceptibly day by day, until there was only a trace present on July 2. The following day it was entirely absent and on the 4th and 5th of July only the most minute trace could be detected.

Summary: In conclusion we should like to point out that so far as we have been able to ascertain, Cases I, II, and III, are the first reported instances of Bence-Jones proteinuria in association with myeloid leukæmia. It has never been observed in the acute forms of the disease, either lymphatic or myeloid, and, including the cases presented here, only eight times in the chronic varieties. The Bence-Jones protein alone was present in Cases I and IV of our series, while Mörner's body also was present in the other two cases, as well as serum albumin in Case III. The excretion of the Bence-Jones body was small in amount, which seems to be characteristic when it occurs apart from multiple myeloma. The chloride output was normal in Case I, which is markedly

different from the condition found in Cases III and IV and in our cases of myelomatosis and carcinomatosis.[1] In Cases I and IV the effect of the benzol treatment is especially noteworthy, in that a marked reduction (Case IV) or eventual disappearance (Case I) of the proteinuria and its associated polyuria, occurred, parallel to the diminution in the leucocytosis and apparent approach of the bone marrow to a more nearly normal condition. It is worth recalling in this connection that our experiments in the benzol poisoning of rabbits failed to bring about an excretion of the Bence-Jones protein.[2] These cases furnish additional confirmation of the previously expressed view, that Bence-Jones proteinuria is not essentially dependent upon one disease, but is a manifestation of disturbances in the bone marrow affecting endogenous metabolism.

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CAUTERIZATION OF "INOPERABLE" CARCINOMA OF THE CERVIX OF THE UTERUS.

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The temporary improvement following an extensive cauterization of advanced carcinoma of the cervix of the uterus has been noted by many surgeons. While the importance of an early diagnosis cannot be overestimated, the larger group, generally classified as "inoperable" cases, is not to be ignored. The result obtained by a thorough cauterization and a subsequent radical abdominal operation seems to justify a detailed report of the following case:

Gyn. No. 16152; Path. Nos. 14307 and 14418.—Mrs. J. was admitted to the clinic on October 27, 1909, complaining of "bleeding from the womb."

Family History.—Negative for tuberculosis and cancer.

Personal History.—Except for an attack of pneumonia, 24 years ago and typhoid fever, 22 years ago, the patient has enjoyed excellent health.

Menstrual History.—Menses began at the age of 13 years; occurring regularly every 4 weeks and lasting about 7 days; no dysmenorrhœa; no intermenstrual bleeding; meno-pause, 5 years ago.

Marital History.—Married 30 years; 8 children; eldest child 29 years; youngest, 12 years; 3 miscarriages, many years ago. Labors and puerperia, normal. No leucorrhœa.

Present Illness.—Patient began to bleed about 6 months before entering the clinic. Previously there had been no leucorrhœa or other symptoms to indicate uterine disturbance. "Spotting" (once in two or three weeks) was first noticed. Gradually, the bleeding became more profuse and about 6 weeks before being admitted, she had a very severe hæmorrhage. The patient became very "dizzy" and fainted many times during the day. Following this attack, she was confined to her bed almost constantly. She consulted a physician two to three months before she came here; he told her the menses were returning. Although no examination was made, he assured her it was not cancer because the discharge didn't have a bad odor. There had been no abdominal pain, no bladder or rectal symptoms.

Physical Examination.—The skin is very sallow; the lips and mucous membranes show a marked pallor; the pupils are equal and react normally.

Pulse, 80 to the minute, regular, fair quality; vessel wall thickened.

Glands: inguinal glands are palpable and very hard.

Chest and abdomen, negative.

Hæmoglobin, 43 per cent (Sahli).

Admission Note. Oct. 29, 1909 (Dr. E. H. Richardson).—The abdomen is slightly scaphoid. There is considerable loss of subcutaneous fat. There is no abdominal tenderness. There are chains of palpable glands in both groins.

Pelvis.—There is a moderate relaxation of the vaginal outlet. The cervix is the seat of a large cauliflower carcinomatous growth about 6 to 8 cm. in diameter. This growth completely encircles the cervix but has not yet involved the anterior vaginal wall or bladder. The right fornix is still soft and the base of the right broad ligament is movable, although it is apparently thickened. Posteriorly and to the left side, the new growth has already involved the vaginal mucous membrane and has extended out to the pelvic wall where the tissues are fixed. The tumor mass is very friable and bleeds readily on manipulation. The body of the uterus is not enlarged. There is a profuse bloody and very offensive discharge.

On account of the free bleeding, a curettage and cauterization of the new growth was done, Nov. 3, 1909.

Operative Note.—Under gas anæsthesia, the examination showed that the carcinomatous growth was advanced to such a stage as to render a complete operation impossible. The cervix was greatly enlarged and large masses of carcinomatous tissue could be torn away with the fingers. It had extended quite out to the pelvic wall on the left side.

The friable portion of the growth was removed by the fingers after which the walls of the vagina were protected with moistened gauze pads. Very hot "soldering irons" were then introduced into the central portion of the growth until it was deeply cauterized on all sides. An iodoform gauze pack was then placed against the cervix.

The patient was returned to the ward and an effort made to improve the general condition by the use of tonics and general hygienic treatment. On November 14, 1909, 11 days after the cauterization, the routine examination was made preparatory to the patient being discharged. Considerable improvement was noted in her general condition and the hæmoglobin had risen to 47 per cent (Sahli). Pelvic examination showed such a "melting away and loosening up" of the carcinomatous growth that a radical operation was advised and done on the following day.

Ether Examination and Operation, November 15, 1909 (Dr. Kelly).—On pelvic examination, the results of the cauterization done two weeks ago were found to be remarkable. The extensive carcinomatous mass at that time occupying the vaginal vault had collapsed very markedly, and the dense induration on either side seemed to have disappeared to a great extent. There was a crater-like opening into the uterus, where the carcinoma had been burned away, so that the index finger could be introduced into the uterine cavity. The adnexæ were quite freely movable.

A hot bichloride douche was used to thoroughly flush out the interior of the uterus and vagina.

A mid-line abdominal incision was made. The pelvic viscera were easily exposed. There were no signs of adhesions about the appendages and the uterus, which was in its lower portion a mere shell, was carefully lifted up. The infundibulo-pelvic and round ligaments on either side were ligated and divided, the broad ligament separated and the ureters exposed without difficulty. It was remarkably easy to dissect the ureters out along the sides of the cervix and to ligate the uterine vessels above them. There seemed to be no carcinomatous involvement whatever about the ureters. The ureters were dissected free, and rolled well out to the lateral walls of the pelvis; the bladder was pushed far down on the vagina, and the utero-sacral ligaments divided well away from the uterus. Clamps were then applied and the parametria excised well out at the pelvic walls.

After sponging out the vagina and "walling off" with gauze on all sides, the Paquelin cautery was used to open the vagina anteriorly well below the growth. Thus the interior of the vagina was brought into view so that the cautery could be applied and the vagina amputated a full centimeter and a half below the margin of the growth on all sides, and the removal of the carcinomatous cervix and the uterus was most satisfactorily accomplished.

The patient was then returned to the ward in very good condition. Her convalescence was entirely uneventful and on Dec. 5, 1909, the following discharge note was made by Dr. Richardson:

Abdominal incision, well healed; no tenderness.

Pelvis.—The vaginal vault is well closed over. There is considerable induration "high up" in the posterior vaginal wall. There are no definite nodules palpable although there is some irregularly in the thickening of the vaginal walls. No tenderness.

Since leaving the hospital, the patient has been entirely free from all symptoms and her physician writes, March 24, 1913 (almost three and one-half years since operation), Mrs. J. is apparently in perfect health. She has grown very stout and does a great deal of hard work.

Path. No. 14418. The cervix has been replaced by a cauliflower growth extending from a point well above the level of the internal os downward onto the vaginal mucosa especially posteriorly and to the left fornix, the excavations on either side having been formed by the previous curettage and cauterization. The exposed surface is seen to be covered by excresences which have resulted from the actively proliferating carcinomatous cells since cauterization. The new growth is surrounded by a thin layer of fairly normal tissue, a wide margin of vaginal mucosa having been removed well below the carcinoma. The upper part of the body of the uterus is atrophic; its muscular walls present the usual appearance and the uterine cavity is lined with the characteristic senile endometrium. The tubes and ovaries are atrophic and show no adhesions.

In determining whether or not any particular case is operable, many things are to be considered. In the first place the general condition of the patient is a very important factor on account of the extensive operation necessary and the usual resulting surgical shock. Since carcinoma is a progressive disease a prolonged course of preparatory treatment is generally not justified, but in certain cases, especially those with little hæmoglobin, the general condition of the patient may be greatly improved by a short delay before operating. Obesity is not necessarily a contra-indication to the radical abdominal operation since, by the employment of the wide horizontal lipectomy described by Kelly, the depth of the field of operation may be greatly decreased, and, if ureteral catheters have been previously placed, the radical operation can be almost as readily completed as in patients of average size.

As regards the local condition, the mobility of the cervix and the new growth is generally considered the most important factor in determining whether or not the extensive operation is advisable. By a thorough microscopic study of the parametria, Kundrat,[1] in 1903, showed that the induration may be due to a secondary inflammatory condition rather than to a carcinomatous infiltration; hence the induration cannot be taken as an infallible sign to determine the operability. Decreased mobility of the cervix in cases of carcinoma of the uterus may be due to three causes, viz: (a) to direct extension of the new growth through the cervix into the broad ligament on either side; (b) to a secondary infection of the carcinomatous area with an inflammatory reaction in one or both broad ligaments; and (c) to an extensive pelvic peritonitis involving one or both broad ligaments. The differential diagnosis of these conditions is often very difficult and an exploratory operation is occasionally necessary to determine the extent of the new growth. Thus from the "Frauenklinik" of Leipsic, out of 221 apparently inoperable cases reported by Aulhorn,[2] 42 cases or about 20 per cent became apparently operable when the exploratory operation was done.

During the past year, an interesting case was reported by Dr. Bumm,[3] as follows:

A patient, 46 years old, suffering from atypical bleeding and pain since February, was admitted to his clinic in May, 1912. On pelvic examination, the cervix was found to be tumid and fixed; there was a large cavity containing broken-down masses, which, on the left side, was in direct continuity with the vagina and the parametrium. On rectal examination, it became evident that a voluminous infiltration extended from the cancerous mass going from the left, posteriorly, to the pelvic wall and rendering the cervix immobile. On account of the diffuse character of the infiltration, a removal of the cancer did not seem possible and the case was assigned to Roentgen treatment because of inoperability.

During June and July, the patient was treated at intervals of one to two days, according to the method described by Dr. Haendly[4] at the June Meeting of the Berlin Gynecological Society. In September, the treatment was resumed. About the middle of October on re-examining the patient, who up to that time had been receiving 800 Holzknecht [X-ray] units, equal to 1600 Kienböck, a marked improvement in the general and local condition was noted. The patient asserted that the bleeding had ceased entirely; that the discharge which had lost its putrescent odor, had diminished, and that the pain had disappeared. Instead of the former large crater-like cavity, there was now only a narrow cavity, in which the penetrating finger found no granulating masses. The cervix was hard and callous; the former diffuse infiltration toward the left side was transformed into a hard

tumor, which was quite separated from the pelvic wall and it and the cervix were now mobile. Operation now seemed possible and was done on October 22, 1912.

At the vaginal preparatory treatment, but little tissue could be scraped away with the sharp spoon, since it came into contact everywhere with a hard grating surface.

After opening the abdominal cavity, the peritoneum was found to be whitish and callous; the tubes and ovaries were agglutinated into one mass with the body of the uterus and could be liberated only with scissors.

The hardening was more marked in the tissues that were more exposed to the rays and it was necessary to liberate the left ureter with scissors from a white glistening callosity. The enucleation of the circumscribed cancerous nodule from the left parametrium was accomplished with ease; on both sides enlarged hard glands were removed from the trunks of the vessels. The convalescence was smooth.

From a clinical standpoint, the case described shows that by vaginal radiation large doses may be administered without causing burns of the mucous membrane; and that under the influence of intense X-rays a hardening of the tissues of the vaginal vault, the cervix and the pelvic connective tissue occurred which both hindered a further dissemination of the cancer and effected a purification of the cancerous crater and a cessation of ichor and hæmorrhage. As a result of the sclerosis of the tissues, the diffuse infiltration of the parametrium became sharply circumscribed from the surrounding structures and the former inoperable cancer became operable.

While the sclerotic changes and the retrogression of the cancer dissemination could also be clearly seen and palpated in the sectioned specimen, the microscopic examination was somewhat disappointing. The lining of the cervical cavity showed everywhere a thin, not visibly changed layer of proliferating cancerous tissue, which was surrounded first by a thin layer of densely infiltrated tissue, and then by an extensive layer of sclerosed connective tissue which almost entirely superseded the muscle bands. In the parametrium and even outside the callous cancer nests of cells were found but the sclerotic glands were free.

A detailed description of this case is given on account of the very close similarity to our case. It is not uncommon to note a temporary relief in certain cases under X-ray treatment and occasionally an inoperable cancer becomes operable. One may ask, Why are the patients operated upon when improvement is evident? In answer to this question, one must determine upon what the improvement depends. Is it an actual improvement in which there is a "retrogression of the cancer-dissemination," or only an apparent retrogression due to a softening of the surrounding tissues which were the seat of a secondary infection? From a microscopic study of the pathological conditions, one is forced to conclude that the improvement is due to the disappearance of the inflammatory products which were primarily the cause of the induration. In Bumm's case, the microscopic examination showed that the cervical wound cavity was lined by a thin layer of proliferating, visibly unchanged cancerous cells although this layer was directly exposed to the strong X-rays at regular intervals for a period of over three months. Beyond this layer there yet remained a thin layer of densely infiltrated tissue and then a voluminous layer of sclerosed connective tissue. As seen from the accompanying illustration of the gross specimen of our case, although the cervical new-growth was extensively cauterized eleven days previously, there are numerous excrescences which on microscopic examination show active cell proliferation. Photomicrograph I illustrates the extensive infiltration of the inflammatory products among the cancer cell-nests, while photomicrograph II shows an equally extensive inflammatory reaction surrounding the outlying cancer cells and muscle bundles.

Except for the coincident pelvic inflammatory disease in Bumm's case, the conditions were practically identical with those of our case. However, the single extensive cauterization apparently accomplished the same result as the prolonged X-ray treatment.

For many years the following method of cauterization of the cancerous area has been employed in this clinic.

The patient is placed in the perineal position and the usual cleansing done. A posterior retractor is then introduced into the vagina and the cervix grasped and drawn forcibly down by means of a tenaculum forceps. The greater part of the visible new growth is removed either by the fingers or a dull curet. The walls of the vagina are then protected by means of wet gauze pads which are held in position by anterior, posterior and lateral retractors and thus expose the cervix together with the carcinomatous growth on all sides. The cervical canal is thoroughly dilated to allow a more thorough cauterization and to determine whether or not a pyometra is present.

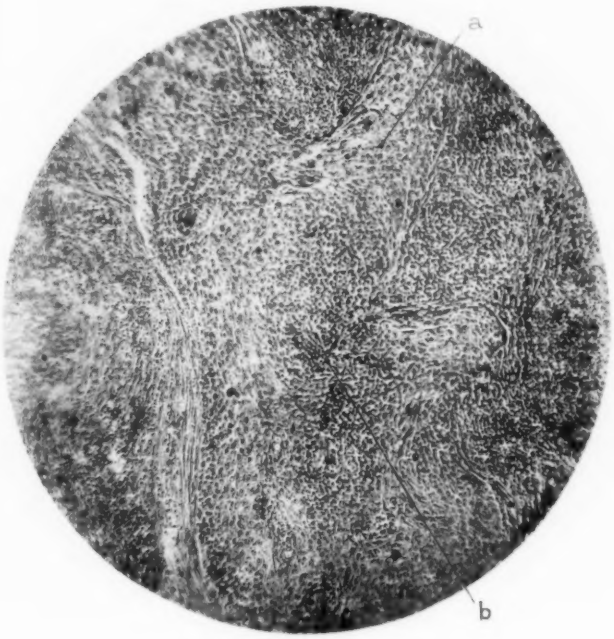
"Soldering irons," as recommended by Drs. William and Charles Mayo, which have been brought to a glowing heat, are then introduced directly into the cervical canal until the carcinomatous growth is thoroughly charred, care being taken not to burn too closely to the bladder and rectum. Occasionally the uterine vessels may be opened, thus giving rise to severe hæmorrhage, necessitating their ligation, but as a rule the bleeding is completely controlled by the charring of the tissues. An iodoform gauze pack is then placed in the vagina and is allowed to remain in position for two to three days. This operation can readily be performed under gas anæsthesia and with practically no shock to the patient.

During the interim between the preliminary operation and the radical abdominal extirpation, an effort should be made to improve the general condition of the patient. Practically all cases of carcinoma of the cervix of the uterus giving rise to symptoms are extensively infected, which renders the ultimate outcome of the operation much more serious; hence, any procedure tending to destroy the local infection is an important factor in the reduction of the percentage of primary mortality. The thorough cauterization should be supplemented by vaginal douches. The technique of disinfection of the vaginal field described recently by the authors[6] has proved very satisfactory; there has not been a single case of peritonitis following the radical abdominal operation where this method has been employed.

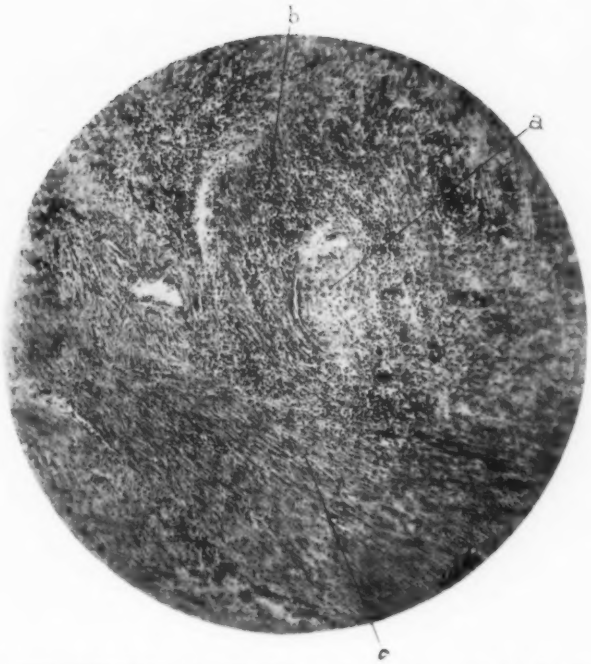
Conclusions

1. The extensive radical abdominal operation offers the greatest hope of absolute cure in patients suffering from carcinoma of the cervix of the uterus.

2. The percentage of operability has gradually increased with the adoption of the radical abdominal operation.



PHOTOMICROGRAPH I.—Showing carcinomatous area seen at *a* and extensive inflammatory infiltration at *b*.



PHOTOMICROGRAPH II.—Showing outlying cancer nest-cells, *a*, and very extensive inflammatory infiltration of the muscle bundles, *b*; the remaining cervical tissue surrounding the new growth is seen at *c*.

Squamous Cell Carcinoma of the Cervex.

3. An exploratory operation is occasionally necessary to determine whether or not the radical operation is to be attempted.

4. Pelvic induration may be due to the following causes: (a) to direct extension of the new growth through the cervix into the broad ligament on either side; (b) to a secondary inflammatory reaction in one or both broad ligaments; and (c) to an extensive pelvic peritonitis involving one or both broad ligaments. Hence the immobility of the cervix is not an infallible sign in determining whether or not a case is operable.

5. In advanced cases of carcinoma of the cervix a preliminary curettage and cauterization is advisable, for the following reasons:

(a) A large portion of the friable new growth may be removed through the vagina.

(b) It is an important procedure in the disinfection of the vaginal field.

(c) The induration in the broad ligaments, due to secondary inflammatory reaction, may be relieved, causing the new growth to become circumscribed and rendering a previously immobile cervix, mobile.

NOTE.—The authors are indebted to Mr. Max Brodel for the illustrations accompanying this paper.

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TESTS FOR HEPATIC FUNCTION: CLINICAL USE OF THE CARBOHYDRATES.

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The discordant and inconclusive results of a series of sugar tests, made in the Medical Clinic of The Johns Hopkins Hospital, suggested that a careful analysis of the methods and results recorded in the prolific, but uncorrelated literature on the subject might throw some light on the clinical value of the carbohydrate tests. The results of this study seem to lead to conclusions quite different from the current ideas.

After a sketch of the literature, a consideration of the theoretical applicability of carbohydrates as tests for liver function, an account of the practical difficulties, and a criticism of the methods as used, an attempt will be made to correlate the findings of the various observers.

LITERATURE.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard immediately stimulated extensive work on carbohydrate metabolism, at first more by pathologists and physiologists, but subsequently by clinicians as well; it was during the course of a heated controversy which waged in the German and French literature, from 1875 to 1900, on the importance of the liver in effecting glycosuria after administration of large amounts of carbohydrates, that the idea of using the sugars as tests for hepatic disease first arose. Quincke,[1] v. Noorden,[2] Kraus and Ludwig,[3] Bloch,[4] and others, representing one side of the question, were unable to demonstrate any constant or marked reduction in sugar tolerance in cases of "liver disease," whereas the French school, especially Roger,[5] Baylac,[6] Bierens de Haen,[7] reported numerous instances of glycosuria after their tests, and championed the use of sugars in studying hepatic function.

The discrepancies in the results of these observers remained unreconciled until Strauss, in a series of papers published in 1898 and the years following, suggested that the use of different sugars in varying amounts probably gave the explanation. Following the technique of the German clinicians he administered[8] 100 gm. of grape sugar in 500 cc. of water on an empty stomach in a series of 38 *Leberkranken*, including carcinoma of the liver, cirrhosis, jaundice, gall-stones, and echinococcus; in only two cases was there a slight transitory glycosuria. In both of these, he remarks, there had been trauma in the liver region. Using, on the other hand, the test meal of the French school, which usually was 150 gm. of cane sugar, he also demonstrated in liver disease a proportion of glycosurias,[9] and felt, on the basis of his work with levulose, that it was this molecule of the cane sugar which was handled with difficulty. Strauss also criticised the interpretation of the reduction tests used in many of the previous observations, and concluded that glucose was particularly inapplicable, inasmuch as there was a mechanism apart from the liver which could handle this sugar. The latter view he supports by experiments of his own on liverless frogs, which he found could still tolerate considerable sugar; in fact, an amount only slightly below their normal tolerance.[8]

In 1901 Strauss[8] followed his sharp criticisms of the older tests by the introduction of levulose. Basing the rationale of his procedure on the work of Sachs,[10] who showed in many experiments that frogs whose livers had been removed had a lower tolerance for levulose than intact controls, a finding which could not be confirmed with dextrose, galactose, or arabinose, he studied a series of cases by the following technique: one hundred grams of levulose were given on an empty stomach, and urine voided during the four following hours was examined by Trommer's and Seliwanoff's tests, fermentation, and polarization. Of 25 cases of "liver disease" *(Leber-*

kranken), cirrhosis 17, cancer 3, complete obstruction 4, "acute cholelithiasis with icterus" 1, amyloid 1, diabetes with cirrhosis 2, 28 or 90% showed an alimentary levulosuria, whereas of 58 individuals either healthy or suffering from ailments not involving the liver, only 6 or 10% put out sugar, and in the latter group he suggests "latent liver disease" as a possible explanation, inasmuch as they suffered from "obesity pototorium, gout, pneumonia, chronic fever, etc." There are no detailed tables, no clinical data, and no confirmation of the diagnoses.

Strauss' test rapidly became popular; the German *Wochenschrifte* during the next ten years abound in brief reports on its application. Ferranini [11] tested 16 cases of "liver disease" by the Strauss method, and subsequently by administration of 100 gm. of grape sugar. His cases included 4 of atrophic cirrhosis, 1 of hypertrophic cirrhosis, 1 of liver lues, 1 "liver stasis icterus with cyst of head of pancreas," 1 of obstructive jaundice in lues, 1 of obstructive jaundice, 3 chronic malarias with enlarged livers, 1 liver cancer, 1 liver sarcoma (?), 1 tumor of left lobe of liver and of the mesentery and of the aorta (carcinoma ?), 1 suppurating echinococcus cyst. He gives no details of the cases, nor any statements as to how the diagnoses were confirmed. In only 1 of these cases was it impossible to demonstrate sugar in the urine after levulose, whereas the glucose test was positive in 10 cases, in 7 of which only minimal amounts were demonstrable by Reals delicate test. He concludes that levulose is a better indication of liver insufficiency than glucose. Bruining [12] also obtained 90% of positive tests among 19 cirrhotics, 11 cases of catarrhal jaundice, and 1 carcinoma ventriculi et hepatis. Landsberg,[13] on the other hand, finds the test of no value after testing 21 cases of liver disease by Strauss' method, of which 9, or 45%, gave a positive test, as did 4 of 7 normals. He suggests as a fallacy that the tolerance varies in normal people. Chajes [14] supports Strauss, finding among 21 *nicht Leberkranken* 19 negative and 2 positive reactions to 100 gm. of levulose. Sabatowski,[15] from a study of 78 cases by Strauss' technique, concludes that cirrhosis, "moderate and severe grades," regularly gives alimentary levulosuria, that chronic passive congestion cases are negative as long as there is no serious destruction of liver substance, that infectious diseases at their height usually give a positive test, that in toxic jaundice there usually is a positive test, but that obstructive jaundice cases are negative unless there is a large destruction of liver. There are no statements as to how information about the extent of the anatomical lesions was obtained. V. Halasz [16] comments on the lack of clinical data in previous reports. Only 1 of 20 normal people put out levulose on 100 gm. Of 12 cirrhotics, 8 were positive; the remaining 4 "were incipient." The test was negative in "fatty liver," "hyperæmia and simple chronic atrophy," in 5 cases of secondary carcinoma, in 1 of catarrhal jaundice, and in 5 of obstructive jaundice. He felt that in doubtful cases a negative test was of value in excluding serious liver disease. Hohlweg [17] found 100 gm. of levulose not tolerated in 6 cases of stone in the common duct, 2 cases of cirrhosis, 1 case of catarrhal jaundice, and 100 gm. tolerated in 3 cases of stones in the gall bladder, 2 cases of sarcoma of liver, 6 cases of secondary malignancy, and 10 cases of chronic passive congestion. Von Frey [18] considered as a positive test one in which 0.1 + gm. of levulose were put out after the administration of 100 gm., and on this basis found of 11 cirrhoses 7 positive, of 3 liver "tumors" none positive, of 4 cases of chronic passive congestion 2 positive, of 2 cases of icterus 1 positive, of 2 cases of hepatic lues 1 positive; 1 fatty liver positive, 1 catarrhal jaundice positive, 1 polycythemia negative. The diagnoses are unconfirmed. Churchman [19] found in 35 cases where the liver was clinically normal 9 positive and 29 negative; in 12 cases where the liver was clinically abnormal, 10 positive and 2 negative, whereas 2 cases clinically doubtful were both positive. He feels that neither a positive nor a negative test is conclusive. Falk and Saxl [20] summarized a large number of cases from the literature and from their own experience, emphasizing the relation between urobilinuria and levulosuria: of 351 cases 259 were positive and 72 negative. No details are given. Finally one should mention the communication of Schmidt,[21] who feels, on the basis of a series of acute febrile cases tested by Strauss' method, that the levulose (and urobilin tests) are of no value in liver disease accompanied by fever, inasmuch as they may be markedly positive without any liver lesions.

Bauer,[22] in 1906, introduced galactose as a liver test in a series of 10 cases of catarrhal jaundice, to whom he administered 40 gm. of galactose in 400-500 cc. of tea in the morning on an empty stomach, and determined quantitatively the amount of sugar put out during the following four to five hours. The cases were tested frequently during the course of the disease and it was found that galactosuria, at first marked, gradually diminished as the condition improved. In 1 case, at the height of the disease, 10 gm. (as much as 25%) was put out. In 12 cases of jaundice due to stones, on the other hand, the galactose output varied only slightly from the normal, the highest being 2 gm. In jaundice due to cancer, galactosuria was usually absent. He concludes that alimentary galactosuria is a constant symptom in catarrhal jaundice, whereas in other liver diseases except in some cases of cirrhosis, and in normals, it is not observed. Bondi and König [23] also found in 8 cases of catarrhal jaundice that, at the height of the disease, after 40 gm. of galactose, 2.0 to 5.9 gm. appeared, and as the patients improved only 0.4-1.8 gm. Falk and Saxl [24] quote 2 cases of cirrhosis. One put out 2.2 gm. on 40 of galactose, the other 0.5 gm. on 20 gm. V. Frey [25] gave 20 gm. of galactose to 8 *Leberkranken* and to 8 people with other diseases. He obtained 1 positive test in each group. Riess and Jehn [26] gave 40 gm. of galactose in a glass of carbonated water. They collected the urine in two 6-hour portions. They considered all cases pathological in which over 2 gm. were put out. On this basis, of 8 cases of gall stones 2 were positive; 5 cases of carcinoma were negative; of 5 cases of "ikterus lueticus" in the secondary period, in 3 the tolerance was not decreased, in 2 moderately so. In chronic passive congestion only 1 of 8 cases was positive. In 15 cases of cirrhosis the tolerance was normal in 9, 3 were on the border line, and in 3 there was a frank

galactosuria. In 17 cases of catarrhal jaundice only 1 mild case reacted normally. All the rest showed galactosuria. In other diseases the only positive result was in a case of croupous pneumonia. They think galactosuria speaks against cancer, chronic passive congestion, and uncomplicated gall stones. Normal tolerance speaks only against catarrhal jaundice. Finally Hirose [25] gave 25 gm. on an empty stomach, the patient already having been on a milk free diet. Of 23 cases 13 were negative, including lues, hepatitis, distomiasis, pseudocirrhosis, choledochus stenosis, icterus with fever, cancer of liver, and gall blader. One chronic passive congestion was negative, 1 positive; 2 cholelithiasis cases were positive, 3 catarrhal jaundice positive, 4 cirrhoses positive. One of the cirrhoses put out 5 gm. In the other positive cases the outputs were all under 2 gm., in most under 0.5 gm. He agrees with Bauer that a positive result is more common in cirrhosis and catarrhal jaundice than otherwise, and that the more diffuse and severe the disease the easier alimentary galactosuria appears.

THEORETICAL APPLICABILITY OF CARBOHYDRATES AS TESTS FOR LIVER FUNCTION.

The newer views in regard to the liver as a center of the carbohydrate-regulating mechanism would seem to alter considerably the rationale of using the sugars as tests for hepatic function. As von Noorden [20] emphasizes, summarizing the results of studies on the glands of internal secretion, one must distinguish on the one hand disturbances in the formation of glycogen by the liver, and on the other disturbances in mobilization of the supply there stored. Cushing, Goetch, and Jacobson,[27] and also Weed, Cushing, and Jacobson,[28] have pointed out that certain lesions of the hypophysis, or of its autonomic nerve supply, are associated with glycogenolysis and glycosuria, whereas under other hypophysical conditions there is a greatly increased sugar tolerance. Similarly, it is known that the internal secretion of the pancreas exerts an inhibitory effect on the mobilization of glycogen by the liver, that the adrenals have an opposite accelerating effect, and that the thyroid less directly partakes in this sugar-regulating mechanism.[29] The studies of Eppinger and Hess [30] on vagotonic and sympathicotonic states, indicate that the facility of glycogen mobilization varies also with the nervous control, and clinically Hirose [25] and Pollitzer [31] quote cases of "neuroses" with low sugar tolerance. It is clear then that disturbance in the fields of the internal secretions, and of the vegetative nervous system may result in a reduced or increased tolerance to carbohydrates without any essential lesion of the liver.

On the side of disturbances in formation of glycogen by the liver due to disease in that organ itself, the carbohydrates should theoretically be applicable as functional tests in so far, at least, as such disturbances might be accompanied by an alimentary glycosuria. The limits of physiological compensation, however, by uninjured liver tissue, or by regenerated cells, is not certain; possibly it may be quite adequate. Clinically, at least, one may see cases of cirrhosis where subsequently, at autopsy, the uninjured liver tissue is found to have undergone marked hyperplasia, compensation evidently having been established until the final break. Furthermore, it is not clear to what extent other tissues may compensate for the liver when that organ is injured, at least in the disposal of carbohydrates. Experimental evidence [10] [32] tends to show that some of the sugars, especially levulose and galactose, are handled almost specifically by the liver. Dextrose tolerance, on the other hand, is not reduced by producing Eck fistulas in dogs [25] and shunting the sugar into the general circulation. At any rate, while the matter is not finally settled, the possibility of compensation by other tissues for deficiencies in the glycogenic function of the liver is quite likely. Therefore, also with anatomical hepatic disease tolerance may be unaltered.

The theoretical basis, then, for the use of sugars as tests for hepatic function is definitely deficient.

PRACTICAL DIFFICULTIES OF CARBOHYDRATE TESTS.

Turning now to the actual application of the sugar tests, a series of practical difficulties immediately arises.

Administration.—Despite all precaution, in a certain number of cases a large dose of sugar sets up nausea, vomiting, or diarrhœa. It has been the experience that in the sicker patients, such as toxic cirrhosis or decompensated cardiac cases, untoward effects were the rule.

Faulty Absorption.—Many of the cases to be examined, particularly cirrhotics, patients with catarrhal jaundice, or with large livers due to chronic passive congestion, present disturbances in the mucosa of the gastro-intestinal tract which tend to render absorption sluggish and may interfere with all of the sugar entering the portal circulation. The presence of these abnormal gastro-intestinal conditions often leads, also, to a fermentation with breaking up of the sugar. The clinical evidence of this fact is ample in the cases where, after administration of sugar, there are frequent movements with great distention and passage of gas.

Portal Obstruction.—Here one encounters, perhaps, the most serious practical difficulty in applying the sugar tests, since it is met with in the most important group to be examined, namely: the cirrhoses. In marked portal obstruction with well-developed collateral circulation, the material absorbed from the intestines does not reach the portal radicles alone, but in part enters the general venous circulation. Under these circumstances one has reproduced conditions similar to those which exist in an Eck fistula dog, where minimal amounts of sugar (levulose, galactose) may result in glycosuria.[33] It is clear, then, that the excretion of sugar in cases of cirrhosis gives no evidence of liver lesion.

Retention of Sugars in Renal Disturbances.—The work of Schlayer and his associates [34] has demonstrated the retention of lactose in certain forms of nephropathy, and the same may hold true of other sugars, although none have been as carefully studied from this point of view. In cases of liver disease with renal complications, which are so common, this may introduce another source of error. Of importance also in this connection is the recent work of Rowntree, Fitz, and Gerachty,[35] showing that the slightest renal congestion causes lactose excretion.

Variable Amounts of Carbohydrate in the Diet.—In determining sugar tolerance on dogs it was found [8] that, to obtain reliable results, the animals must be on a carbohydrate free, or carbohydrate constant, diet, and that the sugar must not be administered oftener than every two days. An amount of sugar far below the tolerance fed on two successive days usually produced glycosuria, the animal being unable to handle a full dose, owing, perhaps, to the glycogen stored from the previous day. In patients, one has no idea of just how much sugar is stored at the time of the test. Hence it may happen that, with a normal liver, a comparatively small amount of sugar would produce glycosuria. The only manner of avoiding this complication would be by having the patient on a constant carbohydrate free diet for several days before the test, and this is unjustifiable in the majority of the cases to be tested.

Criticisms of Methods as Used.

Use of Arbitrary Amounts of Sugars.—Landsberg [13] and Churchman [19] pointed out that the administration of an amount of sugar proportionate to body weight might be more satisfactory than the use of an arbitrary amount. Both, however, followed Strauss' original technique, and we have found no cases reported in which the dose was other than purely arbitrary. Thus, the Strauss method employs 100 gm. of levulose, Bauer [23] and Riess and Jehn [24] gave 40 gm. of galactose, whereas von Frey [18] gave 20 gm. of galactose.

To determine, if possible, just how great an error the use of arbitrary amounts of sugar might introduce, the tolerance of a series of dogs to lactose was determined as carefully as possible.[25] Animals were used rather than ward patients, inasmuch as the dosage and collection of specimens could be better controlled. In a series of sixteen observations on dogs weighing from 6 to 10.6 kilos the tolerance ranged from 1.35 gm. per kilo to 1.6 gm. per kilo, or from 7.5 to 16.5 gm.

In these animals, then, kept under constant identical conditions, and all apparently in good health, it appears that the absolute amount of sugar tolerated varied by more than as much as 100%, roughly in proportion to the body weight.

Now as experimental work [17 18 20 22 25 26] has shown that, apart from acute diffuse massive lesions, liver injuries are accompanied by only slight reductions in sugar tolerance (levulose, lactose, galactose), the threshold of excretion in the doubtful, less marked cases, where the test would naturally be applied, will lie only slightly below normal. Hence, in giving arbitrary amounts of sugar, such as 100 gm. of levulose, a diseased liver in a large man might be unaccompanied by glycosuria, whereas a healthy individual of small tolerance might excrete sugar.

The dogs referred to tolerated roughly 1.5 gm. lactose per kilo of body weight. The possibility naturally suggests itself of calculating the dose for an individual case on this basis. But, as Hofmeister [27] pointed out, the relation of tolerance relative to body weight holds only for animals in average health and in an average state of nutrition. Emaciation, obesity, edema, ascites, do not alter the tolerance proportionally to the change in weight which goes with such conditions. The patients to be examined, however, usually are either emaciated, dropsical, or edematous; hence one cannot calculate a true normal tolerance from their weight, unless by estimation from their previous average weights or by calculations from height and weight tables. But, inasmuch as the reductions in tolerance in disease may be only slight ones, it seems that the only satisfactory method would be to determine directly the normal tolerance in the given individual, a procedure obviously impossible in one already diseased.

While some observers consider the putting out of any sugar after the test as a positive result indicating "hepatic insufficiency," others have assumed that at least a given amount or percentage must be excreted before the test should be counted as positive. In view of what has been said in the previous section, it seems that such a standard only serves still further to complicate the tests and render them more difficult of interpretation.

Finally, one must note that in applying the sugar tests no account has been taken of many of the sources of error mentioned; namely, portal obstruction, renal retention, intestinal fermentation and faulty absorption; nor were the patients on a constant carbohydrate diet.

Discussion of the Results of the Carbohydrate Tests.

Before attempting a comparison of the results of the various sugar tests it is necessary to make clear the exact purpose of the procedures. Is one looking for an index of a disease process in the liver, an anatomical lesion, or a temporary or permanent impairment of liver function? The conception of liver insufficiency is not a simple one; indeed from a clinical view-point such a condition is a rarity. Cases of advanced cirrhosis, with symptoms of general intoxication and showing at autopsy typical hepatic lesions, and some of the acute diffuse liver diseases, such as acute yellow atrophy, Weil's disease, etc., may perhaps be classed as hepatic insufficiencies (although even here the process is too general to ascribe it to one organ alone); but apart from these there are no clinical conditions where it is clear that the organism is suffering from impaired liver function. Even extreme hepatic lesions, such as the red atrophy of chronic passive congestion, luetic infiltrations, and malignant disease, do not present any symptoms which can be directly ascribed to hepatic insufficiency.

It is important to define, then, just what information one expects to gain from a positive sugar test. Throughout the literature confusion exists between "hepatic function" and "liver lesion." The excretion of sugar, according to the standards adopted by various writers, is invariably taken as indicating "hepatic insufficiency," a term which is invariably undefined. And yet, following the doctrine of factors of safety emphasized by Metzer, we know that one-half or more of an organ may be destroyed without interfering with the adequate performance of its function. It should be emphasized, then, that glycosuria after the administration of an amount of sugar which normally should be tolerated, means nothing more than a change in the function of metabolizing sugar. It is quite unjustifiable to take this as evidence of impairment of any other functions of the liver.

What evidence a properly conducted sugar test might offer for or against an anatomical lesion involving destruction of

more or less liver substance, it is hard to say. Theoretically there should be a reduction, but how far compensation by uninjued liver and by other tissues may prevent this is uncertain.

In spite of these theoretical objections, and in spite of the neglect by most writers of the important practical difficulties mentioned, a consideration of clinical reports shows a preponderance of positive tests in those cases classified as suffering from liver disease. The explanation lies, perhaps, in the difficulty of exact clinical diagnosis. In none of the earlier reports, and in only a few of the recent ones, are there adequate data to justify the diagnoses put down. We see, as examples of "liver disease," amyloid liver, diabetes with cirrhosis, "liver stasis with icterus," "fatty liver," "hyperæmia and simple chronic atrophy," none confirmed by operation or autopsy. One writer states that of 12 cirrhotics, 8 gave a positive levulose test and 4 were negative. These four, he states, were "incipient." The positive clinical diagnosis of incipient cirrhosis is, of course, unjustifiable. In several of the earlier reports cases used as controls, but which gave a positive test, were thereupon regarded as suffering from latent liver disease, whereas in obviously diseased livers, with a negative test, compensation by remaining liver substance is resorted to in explanation. The constant finding of a positive galactose test in catarrhal jaundice by various writers seems suggestive, but one cannot reconcile the results of Bauer, using 40 gm., with those of Hirose, who used 25 gm., when the greatest output in Bauer's series was 10 gm. On this basis none of Hirose's cases should have excreted sugar at all.

The preponderance of so-called positive results becomes, then, less significant. When one considers the hopelessly inadequate data furnished in most of the reports, the inclusion in the list of positive cases of many where, in spite of some lesion, no essential disturbance in the liver exists—chronic malarias, hydatid cyst, etc., the inclusion of cases of portal obstruction in the positive reports—it does not seem fair to condemn or support the sugar tests on these statements.

The theoretical deficiencies of carbohydrates as tests for liver function, the use of arbitrary amounts of sugar, the lack of consideration of the disturbing factors, would seem to far outweigh the confused mass of case reports as evidence against the value of the sugar tests.

SUMMARY.

A consideration of the extrahepatic factors involved in the sugar regulating metabolism, the influence of the glands of internal secretion and of the vegetative nervous system, the ability of other tissues than the liver to handle sugar, and the ability of the uninjured liver substance to compensate in disease, make the sugars theoretically unsatisfactory as tests for hepatic insufficiency.

There are a series of great practical difficulties in applying the tests; namely, nausea, vomiting, and diarrhœa after feeding, faulty absorption, intestinal fermentation, portal obstruction with collateral circulation, retention of sugars in nephritis, and inconstancy in the diet.

There are serious objections to the methods as they have been applied; namely, the use of arbitrary amounts of sugar, and the use of a definite standard of excretion.

An analysis of the reports shows their significance to be lessened, owing to confusion in the conception of hepatic insufficiency, insufficient clinical data, and neglect of the practical considerations mentioned.

CONCLUSIONS.

1. Sugars are theoretically unsatisfactory as tests for liver insufficiency.

2. There are difficulties, which appear insurmountable, in the practical application of the tests.

3. The evidence from the clinical reports is not in such form as to prove or disprove the value of the tests.

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TESTS FOR THE HEPATIC FUNCTION: LACTOSE TOLERANCE AS INFLUENCED BY THE LIVER NECROSIS OF CHLOROFORM POISONING.

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Introduction.

In this study an attempt has been made to ascertain to what extent the tolerance for lactose or one of its split products, galactose, is reduced in experimentally produced liver lesions, and to determine whether such a reduction is an index of the degree of liver injury.

Experimental animals are especially favorable subjects for the study of this problem, since, in them, it is possible to control in a large measure the conditions of the metabolism experiment, and to find out the tolerance for a given carbohydrate in health before proceeding to establish the fluctuations in tolerance following liver injury. Although an endeavor was made to use the lactose test in a number of experimental liver lesions, we wish to report in detail only upon the results obtained with this test in liver necrosis produced by chloroform poisoning, and to refer briefly to the other experiments.

The use of chloroform to produce liver impairment and signs of liver insufficiency has many advantages over some of the other classical methods—liver extirpation, portal caval anastomosis, common bile duct ligation, and phosphorous poisoning—all of which have been employed to remove the liver partly or completely from participation in metabolism. It has been shown by Whipple and Sperry [1] that the essential injury of chloroform is in the liver tissue, and that this drug administered by inhalation to dogs for a period of one to two hours will invariably cause central liver necrosis. Moreover, the degree of this necrosis depends upon the duration of the anæsthesia and upon the susceptibility of the animal. In general, the average amount of injury done to a dog's liver by two hours' chloroform anæsthesia is a central necrosis involving about *two-fifths* of the parenchyma of each lobule.

These authors have shown further that from such an injury a liver can recover rapidly. At the end of the period of repair, which begins on the second or third day and is almost complete in six or seven days, the liver tissue regains its normal appearance by a rapid multiplication of the remaining liver cells. This process of repair is unattended by the formation of fibrous tissue.

By the use of chloroform, it is possible to produce an extensive injury in a short time and with a fair degree of certainty. For metabolism experiments, the production of liver injury by this drug has two additional advantages: First, the animal, if not fatally poisoned, will recover from the toxic symptoms in thirty-six to forty-eight hours after the anæsthesia, thus permitting feeding tests to be carried on at a time when the liver necrosis is at its maximum; second, it is possible to study the return of the carbohydrate tolerance to normal after the liver has repaired the injury.

Our experiments seem to indicate that the tolerance for lactose in dogs may be reduced more than 50 per cent through the production of liver necrosis by chloroform anæsthesia. It will be seen also that in non-susceptible animals in whom the injury is only slight, no such reduction in tolerance occurs, and that at the end of the reparatory activity of the liver an animal regains its normal tolerance for lactose. A reduction of the lactose tolerance, therefore, gives some information concerning the degree of liver injury, and this knowledge may prove of value in functional studies of liver disease.

The Use of Lactose.

It was the original intention of the authors to use galactose for these experiments, since, according to Bauer [2,3] and other workers (Posselt,[4] Bondi and Konig,[5] Reiss and Jehn,[6] Hirose [7] and Wörner [8]), this monosaccharide has proved useful as a test for liver function. Because of the great cost of galactose, however, its use is impracticable in experimental work, and would be all the more so were it to be employed as a test in the clinic. Besides, there is sufficient experimental evidence to show that lactose can be used in the place of galactose in feeding experiments in which it is desired to determine the tolerance of the latter, provided suitable conditions exist within the intestinal tract for the cleavage of lactose into its constituent molecules—dextrose and galactose.

The work of Hofmeister,[9] Liezzatto,[10] and our own affords evidence that the reducing body, which appears in the urine of dogs following the administration *per os* of lactose in doses above the assimilation limit, is a monosaccharide whose properties are identical with those of galactose. This Hofmeister showed in two ways: First, following the ingestion of hydrolyzed milk sugar which consists of the molecules dextrose and galactose, dogs show a galactosuria; second, the tolerance of dogs for galactose is quantitatively one-half that for lactose.

Liezzatto [l. c.] was able to confirm this observation. He fed lactose to dogs and subjected the reducing body which appeared in the urine to careful study: fermentation, polariscopic and galactosazone tests, as well as the chemical separation and identification of this carbohydrate. By all of these methods he demonstrated the reducing body to be galactose.

In our experiments, in order to exclude the possibility of a lactosuria, we supplemented the tests of Fehling and of Nylander with one described by Wohlk and also by Malfatti for the demonstration of lactose in the urine.

It has been assumed by those who have used galactose as a

test for liver function that after its absorption from the intestine this monosaccharide, like the others, is converted by the liver into glycogen. This assumption, however, has not been upheld by all workers. A study of the literature shows that only the more recent experimental studies afford evidence that galactose is a glycogen former. From their experiments Kulz [11] and Voit [12] and his school (Otto, Abbot, Lusk) concluded that the organism can form glycogen from dextrose and levulose. As for the other sugars, glycogen could be formed from them only if they were converted in the bowel into dextrose and levulose. This they did not believe to be true of lactose and galactose, which they found unchanged in the fæces.

The later experiments of Kausch and Socin,[13] Weinland,[14] Cremer,[15] and of Murschausen and Hoffmans [16] show that glycogen can be formed from galactose, but to a more limited extent and with greater difficulty than from the other monosaccharides. The discrepancy between these later results and those of the Voit school is due to the difference in the experimental animal used. As Weinland points out, pigeons, chickens, and adult rabbits differ from dogs, in that they lack the intestinal ferment lactase. The Voit school could not demonstrate an increase in glycogen after feeding lactose, because in the animals used by them the lactose was not split in the bowel into its constituent molecules—dextrose and galactose. Later work would seem to indicate, therefore, that feeding lactose to dogs increases the stored glycogen.

The difficulty of its assimilation probably explains the peculiar usefulness of galactose as a test for liver function. The position of this monosaccharide, lowest in the scale of carbohydrate tolerances, suggests that it differs from dextrose in that the bulk of the work of assimilating this molecule is done by the liver. That such is probably the case is shown by the work of Blumenthal.[17] This worker fed dogs the assimilation limit of a given carbohydrate and immediately after tested the power of the animal to handle the same carbohydrate when administered intravenously. He found that fifteen times as much dextrose as galactose could be injected before sugar was detected in the urine. This would seem to indicate that, apart from the liver, other tissues possess only one-fifteenth of the power to assimilate galactose as compared to dextrose. There is, however, no convincing experimental evidence that the liver is the only organ concerned in the conversion of galactose into glycogen, which, according to Sachs,[18] may be true for levulose.

METHODS.

Healthy dogs weighing from 6-10 kilos were used. The animals were kept in special metabolism cages. In such cages specimens of urine can be collected by placing containers beneath them. Before feedings, the cages were cleaned, thus insuring a minimum contamination of the urine.

It is important that the activity and diet of the animals be as nearly constant as possible during the experiment. These factors can be controlled by keeping the dogs in cages throughout an experiment, and by feeding them on a meat diet.

The animals were fed weighed amounts of sugar by stomach tube, sufficient water being introduced through the tube to stimulate diuresis. The feedings were continued with varying amounts of sugar until the tolerance of the animal was determined. Animals should not be fed at too frequent intervals, so as to allow sufficient time for the utilization of the glycogen available from the previous feeding.

Specimens of urine were collected after the feedings. If the urine was contaminated by fæces or vomitus, the results were accepted only if they were negative. It is important to test the first specimen after the feeding, since it usually contains the sugar, if any be excreted. Before each feeding, a control specimen of urine was tested for the presence of sugar.

For the detection of sugar in the urine, the more common tests were used (Fehling, Nylander). In the earlier experiments, in order to exclude the possibility of a lactosuria, a test for the detection of lactose was also used.[1] No quantitative determinations were made.

DETERMINATION OF TOLERANCE.[2]

Before proceeding to determine whether an injury of the liver is associated with a reduction in the tolerance for a given carbohydrate, it is important to know the tolerance for that carbohydrate in health. In clinical cases of liver disease in which a carbohydrate test is done, no such preliminary knowledge is available. This has led to the adoption of arbitrary standards of normal tolerance. For instance, in the levulose test Strauss [19] adopts 100 gm. as a standard and in the galactose test Bauer [l. c.] uses 40 gm.

The use of arbitrary standards of tolerance is open to criticism. It will be seen from Table II that the tolerance in grams varies as the body weight of the animal. In a state of health and under constant conditions of diet and activity this is approximately 1.5 gm. per kilogram of body weight. Hofmeister [l. c.] has pointed out, however, that the estimation of tolerance in grams per kilogram of body weight is not accurate, since the animal varies in weight from time to time, according to its state of nutrition; a condition which should not influence its ability to handle carbohydrates.

This objection applies even more to the use of this method in determining tolerance in pathological states attended by emaciation, dropsy and ascites. For instance, in an experiment in which chronic passive congestion of the viscera and ascites were experimentally produced, the amount of lactose assimilated before and after the operation remained the same, although the animal had gained greatly in weight (11 lbs. to 20 lbs.), due to the accumulation of fluid in the abdominal cavity.

[1] This test, described by Wohlk and by Malfatti, is done as follows: 5 cc. of urine are made alkaline with about 2-5 cc. of strong ammonia and 5 drops potassium hydroxide are added. The mixture is then warmed in the water-bath. In the presence of lactose the solution turns red within five minutes. If dextrose be also present the solution turns reddish brown or brown. With this test the presence of 0.1 per cent lactose can be detected in the urine (Neubauer-Huppert, Analyse des Harns, 1910, I, 459).

[2] By tolerance we mean the largest amount of the sugar which can be fed without causing any to appear in the urine.

Again, the use in clinical cases of an absolute number of grams as a standard of normal tolerance, regardless of body weight, is also open to criticism. It will be noted in Table II that a dog weighing 6 kilograms may be able to assimilate 8-9 gm. as compared to 14-16 gm. for an animal weighing 10 kilograms. From a series of sixteen observations it was found that 10.5 gm. is an average of the normal tolerance. For a dog weighing 6 kilograms, this amount would far exceed the normal, whereas in one weighing 10 or more kilograms this arbitrary standard would fall below the actual tolerance.

In experimental work, where it is possible to establish an animal's normal tolerance preliminary to the production of a liver injury, both of the above objections fall away. Such information is of especial value where the extent of liver injury is small, for in such instances the difference between the assimilation limit in health and in disease may be so slight that the adoption of an arbitrary standard would be misleading. In clinical cases such preliminary tests are not available. The lack of these constitutes a great source of error in the clinical use of the carbohydrates as tests for liver function.

Tolerance of Normal Dogs for Lactose.

Since the literature contains only a few incomplete observations on the normal lactose tolerance of dogs (cf. Table I) the authors have considered it well to tabulate the results of their findings. It will be seen from Table II that the tolerance of normal dogs for lactose is nearly constant (1.5 gm. per kilo)

Table I.—Tolerance of Normal Dogs for Lactose and Galactose According to Various Authors.

Author.	Lactose.		Galactose.	
	Grams.	Grams per kilo.	Grams.	Grams per kilo.
Hofmeister,[l. c.] 1889	1–2	0.4–0.8	0.5–1	0.2–0.4
Liezzatto,[l. c.] 1904	11	1.1	...	0.6
Quartas (Filippi), 1907	...	1.54 males	...	....
	...	3.92 females	...	....
Filippi,[21] 1907	10–15	0.8–1.0	...	....

Table II.—Tolerance of Normal Dogs for Lactose.

No. of dog.	Sex.	Weight in kilos.	Tolerance in grams.	Grams per kilo.	No. of grams above (+) or below (−) tolerance 10.5 gms. standard.
12-90	F.	6.0	9.5	1.60	−1.0
12-89	F.	6.7	11.5	1.65	+1.0
12-80	F.	6.0	8.5	1.40	−2.0
12-76	F.	6.0	8.0	1.35	−2.5
12-73	F.	10.4	16.5	1.55	+6.0
12-58	F.	10.6	14.5	1.38	+4.0
12-2	F.	7.0	11.5	1.60	+1.0
12-44	F.	6.0	8.5	1.40	−2.0
12-54	F.	8.6	13.0	1.50	+2.5
12-38	F.	6.1	8.5	1.40	−2.0
12-3	M.	8.0	12.5	1.55	+2.0
12-121	F.	5.9	9.5	1.60	−1.0
R-I	F.	6.7	7.5	1.10	−3.0
R-II	F.	5.4	7.5	1.38	−3.0
R-III	F.	9.0	12.5	1.40	+2.0
12-122	F.	6.5	9.5	1.40	−1.0
	Average		10.5	1.45	

when estimated in kilograms per body weight, but that wide variations exist in the absolute number of grams used. Our results agree very closely with those of Liezzatto [l. c.] and of Quartas [20] for male dogs, but they do not confirm the finding of the latter that females will tolerate twice as much lactose as males.

Lactose Tolerance in Experimental Liver Lesions.

Attention has been called to the advantages of using chloroform for the production of liver injury, and brief mention has been made of the reduced tolerance for lactose observed after chloroform poisoning. Before giving in more detail the results of these and other experiments, we wish to refer briefly to the observations of others in regard to the effect of experimental liver injuries upon the tolerance for carbohydrates.

Minkowski [22] (1886) was among the early investigators to study the effect of liver extirpation (in birds) upon metabolism. He found the tolerance for dextrose reduced.

Sachs [l. c.] demonstrated that following liver extirpation in frogs the levulose tolerance is decreased, while that of dextrose, galactose and arabinose remains unchanged.

According to Filippi,[l. c.] Eck fistula dogs can tolerate as much starch as normal dogs, but in them the tolerance for all sugars is reduced. Only one-half the amount of lactose and one-third the amount of levulose will be assimilated.

Hohlweg [23] (1909) and v. Frey [24] (1911) each demonstrated reduced tolerance for levulose in rabbits, both after phosphorus poisoning and after ligation of the common bile duct.

Roubitschek [25] (1912) and Wörner [l. c.] (1913) showed that phosphorus poisoning in rabbits causes a reduction in the galactose tolerance. The former fed galactose and the latter injected it into the portal vein, so as to do away with the possibility of faulty intestinal absorption.

Reiss and Jehn [l. c.] (1912) found that the galactose tolerance in dogs is not lowered after ligation of the common bile duct. They point out that in dogs ligation of the duct does not produce any liver injury unless the pancreas also be injured (Fischer, Deut. Arch. f. klin. Med. 1910, C, 329: ibid., 1911, CIII, 157).

Eck Fistula.

The clinical symptoms of an Eck fistula dog suggest that weeks after the operation, when the dog is in good health and well nourished, the animal is not suffering from any marked degree of hepatic insufficiency. It is known (Voegtlin and Bernheim, Whipple and Sperry) that the liver in the early stages does undergo slow atrophy with some fatty degeneration as a result of the scanty blood supply. It is not unlikely that the return of the functional activity of such a liver to normal after a longer period is due to the remarkable reserve capacity of the liver, aided by the establishment of a collateral circulation.

In two experiments with Eck fistula dogs, the lactose tolerance was found reduced to about one-half the normal. This agrees with the observation of Filippi. There is a fallacy,

however, in concluding that the reduced tolerance for lactose is the result of liver injury. One cannot exclude the possibility that only a part of the sugar reached the liver by way of the hepatic arteries and that the remainder made its way into the systemic circulation and was excreted by the kidneys.

The experiments are cited rather to emphasize a point already made, namely, that the galactose molecule is in large part handled by the liver. It will be noted from the protocols and the Tables III and IV that in both animals the tolerance for dextrose remained high even after the production of the fistula, whereas that of lactose was reduced one-half. This would seem to indicate that other tissues were still assimilating the dextrose molecule well, whereas the assimilability of the galactose fraction of the lactose was reduced, as would be expected, in proportion to the amount of liver tissue removed from the general metabolism by the portal caval anastomosis.

Dog 12-2.—Black and tan mongrel, female, 15½ lbs. (7 kilos).

Jan. 25. Lactose 10.5 gm. Urine negative for sugar.

Jan. 29. Lactose 12 gm. Urine clear. Sugar positive. Tolerance 11 gm. lactose.

Feb. 1. *Operation.*—Ether anæsthesia. Portal caval anastamosis.

Feb. 2. Animal is in good condition.

Feb. 10. A. m., lactose 7 gm. Urine positive for sugar.

Feb. 13. Urine negative for sugar (control). Lactose 6 gm. Urine positive for sugar.

March 10. Lactose 4 gm. (63 per cent reduction). Urine negative for sugar.

March 12. 9.30 a. m., galactose 3 gm. 4 p. m., urine clear. Sugar positive.

March 16. Galactose 2 gm. Urine positive for sugar. Tolerance of galactose less than one-half that of lactose.

March 20. Dextrose 20 gm. Urine negative for sugar.

April 2. Phenoltetrachlorphthalein excretion 17 per cent.

As the animal's condition improved this excretion gradually rose, reaching 40 per cent on June 18 (Dr. Whipple). Thus it would appear that the hepatic function, as indicated by the lowered phthalein output (35-50 per cent for normal dogs), was actually diminished about the same time when the lactose tolerance was reduced to one-half.

TABLE III.—Dog 12-2.

Sugar.	Date.	Sugar in grams.	Grams per kilo.	Sugar in urine.	Remarks.
Lactose	Jan. 25	10.5	1.5	+	
	Jan. 29	12.0	1.7	+	Tolerance 11 gm. (1.5 per kilo).
	Feb. 1	*			Good recovery.
	Feb. 10	7	1.0	+	36% reduction.
	Feb. 13	6	0.85	+	45% reduction.
	March 10	4	0.57	0	63% reduction.
					Tolerance 5 gm. (0.7 per kilo).
Galactose...	March 12	3	0.42	+	
	March 13	2	0.28	+	
	March 16	2	0.28	+	Tolerance 2 gm. (0.3 per kilo).
Dextrose ...	March 20	20	2.8	0	Tolerance below 20 gm.

* Operation: Eck fistula.

Dog 61.—Fox terrier, female, 13 lbs. (6 kilos).

March 12, 1912. *Operation.*—Portal vein ligated.

Nov. 25, 1913. Animal is healthy and active. Lactose 6 gm. Urine clear. Sugar positive. No diarrhœa.

Nov. 27. Lactose 3 gm. (0.5 gm. per kilo). Urine obtained 6 hours later is clear and negative for sugar. Estimated tolerance 4.5 gm. Lactose (0.8 gm. per kilo).

Dec. 2. Galactose 3 gm. Urine clear. Sugar positive.

Dec. 3. Galactose 2 gm. Urine clear. Sugar negative. Tolerance 2.5 gm. galactose (0.4 gm. per kilo).

Dec. 4. Dextrose 9 gm. Urine negative for sugar.

Dec. 5, 6, 7, 8. Dextrose 12, 15, 18, and 24 gm. successively. Urine in each case negative for sugar. Tolerance for dextrose above 24 gm.

April 5. Phenoltetrachlorphthalein excretion 45 per cent (Dr. Whipple).

It would appear that at this time the functional capacity of the liver as indicated by this test had nearly reached normal.

TABLE IV.—Dog 61.

Sugar.	Date.	Weight in grams.	Grams per kilo.	Sugar in urine.	Remarks.
Lactose	Nov. 25	6	1.0	+	
	Nov. 27	3	0.5	0	Tolerance 4.5 gm. (0.8 per kilo).
Galactose...	Dec. 2	3	0.5	+	
	Dec. 3	2	0.33	0	Tolerance 2.5 gm. (0.4 per kilo).
Dextrose ...	Dec. 4	9	1.5	0	
	Dec. 6	12	2.0	0	
	Dec. 7	18	3.0	0	
	Dec. 8	24	4.0	0	Tolerance above 24 gm.

CHLOROFORM POISONING.

METHOD.

The normal tolerance of an animal was determined by the method already described. Chloroform anæsthesia was then administered for a period of about two hours. About 36-40 hours after the anæsthesia the animal was fed by stomach tube an amount of lactose which was below the normal tolerance. The urine voided after this feeding was tested for sugar. Before each feeding the urine was tested to make certain that it was sugar free.

In order to correlate the knowledge gained of the functional activity of the liver from the lactose test with the amount of injury done, a piece of liver tissue for microscopical section was removed under ether anæsthesia and with aseptic precautions. The animal was then allowed to repair the liver injury for a period of a week or ten days and the experiment was repeated with a larger or smaller reduction in the quantity of lactose, depending upon the results of the previous test.

EXPERIMENTS.

In one instance an experiment as described above was done four times upon the same animal. The observations upon this animal (dog 12-121) will be summarized, since they are complete and are like most of the others. This dog, a healthy female, was found to have a tolerance of 9.5 gm. lactose. After a 2½ hours anæsthesia the animal was quite ill and the urine the next morning contained a little sugar, which disappeared

on the evening of the same day. This is one of the few instances in which sugar was found in the urine after chloroform anæsthesia (meat diet). About forty hours after the anæsthesia the dog was fed 6½ gm. lactose, which represented a reduction of 33 per cent of its normal tolerance. On this amount, sugar appeared in the first voiding about seven hours later.

The animal was tested again a week after the first anæsthesia. It was found that coincident with the repair of the liver injury the lactose tolerance had returned to normal. Chloroform anæsthesia was then administered for 1¾ hours, an interval of forty hours was allowed to elapse and 6.4 gm. lactose were administered. Again the animal excreted sugar in the urine. A piece of liver removed about ten hours after the test feeding showed a central necrosis involving one-fifth to one-third of each lobule. Nine days later the experiment was repeated with a 50 per cent reduction of the lactose, and finally after a similar interval a fourth test was done with a 60 per cent reduction. After the 50 per cent reduction sugar appeared in the urine, but failed to appear after the 60 per cent reduction.

It may be assumed from the liver tissue removed after the second anæsthesia, that in this particular animal the administration of two hours chloroform by inhalation was sufficient to produce a liver necrosis involving one-fifth to one-third of the parenchyma of each lobule, and that at least this amount of liver injury was present in Experiment C when a 50 per cent reduction was still attended by the presence of sugar in the urine.

This experiment in connection with some of the others cited below makes it fairly certain that following a chloroform anæsthesia of two hours the tolerance for lactose may be reduced at least 50 per cent. The reduction of the functional activity as indicated by the lactose test corresponds fairly closely to the degree of injury demonstrable microscopically.

Dog 12-121.—Brown, female, fox terrier, 13 lbs. (5.9 kilos).

Experiment A.—May 30. A. m., lactose 9 gm. P. m., urine clear, negative for sugar. No vomiting or diarrhœa.

June 1. 10 a. m., lactose 10 gm. 3.30 p. m., urine clear; sugar positive. Tolerance 9.5 gm. lactose.

June 9. 2-4.30 p. m., *chloroform anæsthesia 2½ hours; 1¼ ounces;* well taken.

June 10. Animal looks ill; purulent conjunctivitis of both eyes; slight jaundice; does not eat. A. m., urine gives atypical reaction for sugar. 10 p. m., urine (control) negative for sugar.

June 11. 10 a. m., lactose 6.5 gm. (33 per cent reduction of tolerance). 5 p. m., urine clear; sugar positive. Second voiding negative for sugar.

Experiment B.—June 16. 3 p. m., weight 10 lbs. Lactose 8 gm. P. m., clear urine; sugar negative.

June 18. A. m., lactose 9 gm. Urine clear; sugar positive. Tolerance 8.5 gm. lactose.

June 21. 4 p. m., *chloroform anæsthesia 1¾ hours; 1 ounce;* poorly taken. Vomited at end of anæsthesia.

June 22. Animal looks dull; vomits; does not eat.

June 23. 9.30 a. m., urine clear. Negative for sugar (control). Lactose 6.4 gm. (25 per cent reduction). 5 p. m., urine clear, positive for sugar.

Operation.—8.30 p. m., ether anæsthesia. Incision made through the right rectus; liver was exposed and wedge-shaped piece removed and placed in formalin for histological study. Cut surfaces of liver tissue were approximated by ligature.

Liver.—Microscopical section. Repair of first injury not complete. Central necrosis involving *one-fifth to one-third of each liver lobule.* Middle zone shows rather diffuse, fatty degeneration. Mitotic figures are very numerous.

June 25-30. Animal more active; eats well; is evidently repairing injury. Stitches removed; wound healed.

Experiment C.—July 5. Animal has recovered completely. *Chloroform anæsthesia 2 hours; 1 ounce.* Vomited at end of anæsthesia.

July 6. A. m., dog looks ill; does not eat. Urine negative for sugar.

July 7. 10 a. m., dog a little more active. Urine (control) negative for sugar. Lactose 4.2 gm. (50 per cent reduction). 4 p. m., urine positive for sugar. 9 p. m., urine still positive for sugar.

Experiment D.—July 15. A. m., lactose 7 gm. P. m., urine clear, negative for sugar. Tolerance has evidently risen to normal.

July 17. *Chloroform anæsthesia 2 hours; 1¾ ounces.* Vomited.

July 19. A. m., urine (control) negative for sugar. Lactose 3 gm. (64 per cent reduction). P. m., urine clear; negative for sugar.

TABLE V.—DOG 12-121.

Date.	Chlorof'm.	Lactose in gm.	Sugar in urine.	Remarks.
		EXPERIMENT A.		
May 30..	....	9	0	
June 1...	....	10	+	Tolerance 9.5 gm.
June 9...	2½ hrs.	....	0	No post anæsthetic glycosuria.
June 11..	....	6.5	+	Control negative; 33% reduction of tolerance.
		EXPERIMENT B.		
June 16..	....	8	0	Period of repair one week.
June 18..	....	9	+	Tolerance 8.5 gm.
June 21..	1¾ hrs.	....	0	No post anæsthetic glycosuria.
June 23..	....	6.4	+	25% reduction of tolerance. Operation. Control 0.
		EXPERIMENT C.		
July 5...	2 hrs.	....	0	Period of repair two weeks.
July 7...	....	4.2	+	50% reduction of tolerance.
		EXPERIMENT D.		
July 15..	....	7	0	Period of repair 10 days.
July 17..	2 hrs.	....	0	No post anæsthetic glycosuria.
July 19..	....	3	0	64% reduction of tolerance. Control 0.

Dog R-I.—Brown, female hound, 14¾ lbs. (6.7 kilos).

Experiment A.—June 23. 9.30 a. m., lactose 9 gm.; 5.30 p. m., urine positive for sugar.

June 25. 9.30 a. m., lactose 8 gm. P. m., urine clear. Sugar positive.

June 28. 9.30 a. m., lactose 7 gm. P. m., clear urine; negative for sugar. Tolerance 7.5 gm. lactose.

July 5. *Chloroform anæsthesia 2 hours; 1 ounce;* well taken.

July 6. A. m., animal drowsy; but not extremely ill. Slight

jaundice of scleræ and mucous membranes. No vomiting. Urine (control) negative for sugar.

July 7. 10 a. m., lactose 4.5 gm. (40 per cent reduction). 4 p. m., urine, clear specimen; sugar positive. 9 p. m., next voiding, sugar negative.

Operation.—9 p. m., piece of liver tissue removed for study. Wound very moist; considerable oozing.[3]

Liver.—Microscopic section. Central necrosis involving three-fifths of the cells of the liver lobule. There is a very thin middle zone of fatty degeneration. About the portal areas, nearly one-third of the parenchyma is pretty normal.

July 9. Animal in good condition; wound is healing.

Experiment B.—July 15. Lactose 7 gm. P. m., urine negative for sugar. Tolerance evidently risen to normal.

July 17. *Chloroform anæsthesia 2 hours; ¾ ounce.*

July 19. Animal dull; does not eat. Urine (control) negative for sugar. 10 a. m., lactose 3 gm. (60 per cent reduction). 4 p. m., urine negative.

TABLE VI.—DOG R-I.

Date.	Chlorof'm.	Lactose in gm.	Sugar in urine.	Remarks.
		EXPERIMENT A.		
June 23..	....	9	+	
June 25..	....	8	+	
June 28..	....	7	0	Tolerance 7.5 gm.
July 5...	2 hrs.	....	0	No post anæsthetic glycosuria.
July 7...	....	4.5	+	40% reduction of tolerance. Operation. Control 0.
		EXPERIMENT B.		
July 15..	....	7	0	Period of repair 8 days.
July 17..	2 hrs.	....	0	No post anæsthetic glycosuria.
July 19..	....	3	0	60% reduction of tolerance. Control 0.

Dog R-II.—Spotted, white female hound, 12 lbs. (5.4 kilos).

Experiment A.—July 10. A. m., lactose 7 gm. P. m., urine clear. Sugar negative.

July 12. A. m., lactose 8 gm. P. m., urine clear. Sugar positive. Tolerance 7.5 gm. lactose.

July 14. *Chloroform anæsthesia 2 hours; ¾ ounce;* well taken.

July 15. Animal dull. A. m., urine shows presence of sugar. P. m., sugar absent in second voiding.

July 16. Lactose 3.5 gm. (50 per cent reduction). P. m., urine clear; positive for sugar.

Operation.—8.30 p. m., piece of liver tissue removed in usual way.

Liver.—Microscopic section. Central necrosis involving about *three-fifths* of each liver lobule; practically no fatty zone. Marginal parenchyma shows a little diffuse, fatty degeneration with fine fat droplets in the protoplasm. Mitotic figures visible.

July 18. Animal more active.

Experiment B.—July 21. Animal is evidently repairing injury. Lactose 6.5 gm. P. m., urine clear and negative for sugar. Tolerance is rising to normal.

July 22. *Chloroform anæsthesia 2 hours; 1 ounce;* well taken.

July 23. Dog dull; vomited. Urine negative for sugar.

[3] It has been shown by Whipple and Hurwitz (J. Exp. M., 1911, XIII, 136) that the hæmorrhages of chloroform poisoning are due to inefficient coagulation resulting from a decrease in the fibrinogen of the blood.

July 25. A. m., lactose 2.5 gm. (65 per cent reduction). P. m., urine clear. Sugar positive.

TABLE VII.—DOG R-II.

Date.	Chlorof'm.	Lactose in grams.	Sugar in urine.	Remarks.
		EXPERIMENT A.		
July 10..	....	7	0	
July 12..	....	8	+	Tolerance 7.5 gm.
July 14..	2 hrs.	....	+	Sugar present in first voiding after anæsthesia.
July 16..	....	3.5	+	50% reduction in tolerance. Operation. Control 0.
		EXPERIMENT B.		
July 21..	....	6.5	0	Period of repair one week.
July 22..	2 hrs.	....	0	No post anæsthetic glycosuria.
July 25..	....	2.5	+	65% reduction of tolerance. Control 0.

This animal (Dog R-II), it appears, was particularly susceptible to chloroform poisoning; a two-hour anæsthesia producing a central necrosis involving *three-fifths* of each liver lobule. At this time the animal excreted sugar, although the quantity of lactose administered was only one-half its normal tolerance. On a second occasion, and with probably the same extent of liver injury, this dog put out sugar in the urine after a 65 per cent reduction of the quantity assimilated in health.

Dog R-III.—Spotted, white, female hound, 20 lbs. (9 kilos).

Experiment A.—July 10. 10 a. m., lactose 12 gm. P. m., urine clear; sugar negative.

July 12. Lactose 13 gm. P. m., urine clear; positive for sugar. Tolerance 12.5 gm. lactose.

July 14. *Chloroform anæsthesia 2 hours; ¾ ounce;* well taken.

July 15. Dog looks active. Urine: Specimens a. m. and p. m., both negative for sugar (control).

July 16. Lactose 5 gm. (60 per cent reduction). P. m., urine gives reaction for sugar.

Operation.—9 p. m., piece of liver removed in usual way.

Liver.—Microscopic section. Lobules show central necrosis involving *one-half* to *three-fifths* of the liver cells. There is a thin middle zone of fatty degeneration. About one-fifth of each lobule is practically normal.

TABLE VIII.—DOG R-III.

Date.	Chlorof'm.	Lactose in gm.	Sugar in urine.	Remarks.
		EXPERIMENT A.		
July 10..	....	12	0	
July 12..	....	13	+	Tolerance 12.5 gm.
July 14..	2 hrs.	....	0	No post anæsthetic glycosuria.
July 16..	....	5	+	60% reduction of tolerance. Operation. Control 0.
		EXPERIMENT B.		
July 21..	....	11.5	0	Period of repair one week.
July 22..	2 hrs.	....	0	No post anæsthetic glycosuria.
July 24..	....	5	+	60% reduction of tolerance. Control 0.

Experiment B.—July 21. Dog is quite active; evidently is repairing injury. A. m., lactose 11.5 gm. P. m., urine negative for sugar. Tolerance rising to normal.

July 22. *Chloroform anæsthesia 2 hours; one ounce.*

July 23. Animal drowsy; does not eat; vomited.

July 24. Urine (control) negative for sugar. A. m., lactose 5 gm. (60 per cent reduction). P. m., urine gives sugar reaction.

In this experiment (Dog R-III) the observations were repeated twice under exactly the same conditions with the same results. In the first instance, and probably also in the second, a two-hour anæsthesia caused a central necrosis involving one-half to three-fifths of the liver cells. At this time the functional activity of the liver was probably low, as was indicated by the presence of sugar in the urine following the administration of only 60 per cent of the amount of lactose which the animal tolerated before the anæsthesia.

Dog 73.—Black and white mongrel, female, 23 lbs. (10.4 kilos).

Feb. 19. 9.30 a. m., lactose 15 gm. P. m., urine: Sugar negative.

Feb. 24. Lactose 16 gm. Urine: Sugar negative.

Feb. 25. 10.30 a. m., lactose 17 gm. P. m., urine clear. Sugar positive. Tolerance 16.5 gm. lactose. Repeated Feb. 28, with same result.

March 6. *Chloroform anæsthesia 2 hours; 1 ounce;* well taken.

March 7. Dog is dull; vomited.

March 8. Animal still ill. Urine (control) negative for sugar. 9.30 a. m., lactose 15.5 gm. (7 per cent reduction). 5 p. m., specimen of clear urine is positive for sugar; lactose test negative. Urine from next voiding negative for sugar.

Operation.—8 p. m., ether anæsthesia. Piece of liver removed in the usual way. Wound is moist, and there is considerable oozing.

Liver.—Microscopical section. Central necrosis involving from two-fifths to one-half of the liver lobule. There is a middle zone of fatty degeneration. Mitotic figures are numerous.

Dog 12-38.—Small yellow mongrel, female, 13½ lbs. (6.1 kilos).

Experiment A.—Dec. 23. Lactose 12 gm. Urine clear. Sugar positive.

Dec. 27. Lactose 11 gm. Urine clear. Sugar positive. No diarrhœa.

Jan. 5. Lactose 9 gm. Urine positive for sugar.

Jan. 11. Lactose 8 gm. Urine negative for sugar. Tolerance 8.5 gm. lactose.

Jan. 14. *Chloroform anæsthesia 1¾ hours.*

Jan. 15. Animal in good condition. Urine negative for sugar.

Jan. 16. Lactose 7 gm. (17 per cent reduction). Urine negative for sugar.

Jan. 22. *Chloroform anæsthesia 2¾ hours; 2¼ ounces;* not well taken.

Jan. 24. Dog dull A. m., lactose 7 gm. Urine, catheterized specimen positive for sugar. No sugar in voidings during same day.

Operation.—Piece of liver removed in usual way.

Liver.—Microscopical section. Repair is not complete. Injury involves about central *one-third* of each lobule. Middle zone shows pronounced fatty degeneration involving one-fifth of the lobule. Wandering cells everywhere numerous.

Experiment B.—Feb. 6. Animal seems well; injury is evidently repaired. A. m., lactose 7 gm. Urine negative for sugar. Normal tolerance returning.

Feb. 17. *Chloroform anæsthesia 2¼ hours; 1⅛ ounces.*

Feb. 19. A. m., lactose 7 gm. Urine positive for sugar.

This animal (Dog 12-38) showed some resistance to chloroform poisoning. After a 1¾ hours' anæsthesia no sugar appeared in the urine, even though the normal tolerance was reduced only 17 per cent. A week later, however, an anæsthesia of 2¾ hours did result in a liver necrosis involving one-third of each lobule.[4] Now the administration of the same amount of lactose was attended by the appearance of sugar in the urine. A repetition of this experiment about two weeks later gave the same result.

Dog 12-30.—Fox terrier, male. 19.8 lbs. (9 kilos).

Dec. 6. Lactose 18 gm. Urine shows the presence of sugar; but reaction is only slight. Tolerance estimated at 17 gm. lactose.

Dec. 8. *Chloroform anæsthesia 1½ hours; ⅞ ounce.*

Dec. 9. Animal looks fairly active; has not vomited. Urine clear; negative for sugar (control).

Dec. 10. A. m., lactose 11 gm. (35 per cent reduction). P. m., large quantity of clear urine. Sugar negative.

Dec. 11. *Chloroform anæsthesia 1 hour; ½ ounce.*

Dec. 12. Animal does not look ill. Urine negative for sugar (control).

Dec. 13. A. m., lactose 11 gm. (35 per cent reduction). P. m., specimen of clear urine shows no sugar.

Operation.—8 p. m., piece of liver tissue removed in usual way.

Liver.—Microscopical section. Repair of previous injury is almost perfect. There is no definite necrosis, and little central fatty degeneration.

Dog 12-27.—Fox terrier, female, 24 lbs. (11 kilos).

Nov. 29. Lactose 25 gm. Urine positive for sugar.

Nov. 30. Lactose 22 gm. Urine positive for sugar.

Dec. 2. Lactose 17 gm. Urine negative for sugar. Estimated tolerance 19 gm. lactose.

Dec. 5, 6, 7, and 8. Glucose 22, 27, 33, and 44 gms. given successively without producing a glycosuria. Tolerance for glucose 44 gm. plus.

Dec. 8. 9.30 p. m., *chloroform anæsthesia 1 hour; ⅛ ounce.*

Dec. 9. Dog in good condition. Urine positive for sugar—post anæsthetic (?). 9 p. m., urine negative for sugar (control).

Dec. 10. Lactose 13 gm. (31 per cent reduction). Urine several hours later clear and negative for sugar.

Dec. 11. 3.30 p. m., *chloroform anæsthesia 1 hour; 1 ounce.*

Dec. 12. Animal looks drowsy. Urine negative for sugar (control).

Dec. 13. 12 m., lactose 13 gm. (31 per cent reduction). Diarrhœa.

Dog 12-3.—Bull terrier, male, 16 lbs. (7.3 kilos).

Dec. 3. Lactose 11 gm. Urine clear. Sugar positive. No diarrhœa.

Dec. 5. Lactose 15 gm. Urine contaminated.

Jan. 25. Lactose 13 gm. Urine clear; faint reduction to Fehling's solution. Tolerance 12 gm.

Feb. 3. *Chloroform anæsthesia 3 hours.*

Feb. 5. Lactose 11.5 gm. (11 per cent reduction). Urine clear. Sugar negative.

Dogs 12-30, 12-27, and 12-3 also showed some resistance to chloroform poisoning.

In dog 12-30 a 1½ hour anæsthesia did not produce sufficient liver injury to lower the lactose tolerance 35 per cent. An additional anæsthesia of one hour administered two days later did not produce any appreciable necrosis, and a lactose test showed that the tolerance was not reduced.

[4] The only slight injury observed in this and other animals following an anæsthesia of such duration is due to the repetition of the anæsthesia before the liver injury resulting from the first was complete. It is known that during repair the liver is resistent to chloroform poisoning.

TABLE IX.—SUMMARY OF CHLOROFORM EXPERIMENTS.

Number of dog.	Normal tolerance.	Duration of anæsthesia.	Sugar in urine.	Reduction of tolerance.	Per cent of reduction.	Extent of liver injury.
12-73	16.5	2 hrs.	+	1.5	7	⅔ to ½ lobule
12-3	13.0	3 hrs.	0	1.5	11	.....
12-38	8.5	1¾ hrs.	0	1.5	17	.....
	8.5	2¼ hrs.	+	1.5	17	⅓ of lobule
12-38 B	8.5	2¼ hrs.	+	1.5	17	.....
12-27	19.0	1 hr.	0	6.0	31	.....
12-30	17.0	1½ hrs.	0	6.0	35	.....
	17.0	1 hr.	0	6.0	35	No necrosis
12-121 A	9.5	2½ hrs.	+	3.0	33	.....
12-121 B	8.5	1¾ hrs.	+	2.0	25	⅓ to ½ lobule
12-121 C	8.5	2 hrs.	+	4.3	50	.....
12-121 D	8.5	2 hrs.	0	5.5	64	.....
R_1-A	7.5	2 hrs.	+	3.0	40	⅔ lobule
R_1-B	7.5	2 hrs.	0	4.5	60	.....
R_2-A	7.5	2 hrs.	+	3.5	50	⅔ lobule
R_2-B	7.5	2 hrs.	+	5.0	65	.....
R_3-A	12.5	2 hrs.	+	7.5	60	½ to ⅔ lobule
R_3-B	12.5	2 hrs.	+	7.5	60	.....

OTHER LIVER LESIONS.

Experiments were made to determine whether the lactose tolerance was reduced after phosphorus poisoning and after ligation of the common bile duct. These observations are not complete and no definite conclusions can be drawn from them.

The following experiment (dog 12-44) is of interest because of the application of this test to an animal in which experimental passive congestion had been successfully produced.

Dog 12-44.—Irish poodle, female, 13 lbs. (5.9 kilos).

Jan. 19. 10 a. m., lactose 8 gm. Urine negative for sugar.

Jan. 20. 9 a. m., lactose 9 gm. Urine faintly positive for sugar. Tolerance 8.5 gm. lactose.

Jan. 21. *Operation.*—(Dr. McClure): Stitches placed in inferior vena cava just above diaphragm; lumen narrowed to 2-3 mm. in diameter.

Jan. 23. Animal made good recovery from operation. Wound is healing. Lactose 8 gm. Urine negative for sugar.

Jan. 31. Marked generalized œdema of tissues of back, legs and abdominal walls; abdomen swollen and tense. Weight 19¾ pounds.

Feb. 1, 4, 6, and 7. Repeated abdominal tappings. More than 5 litres of ascitic fluid removed.

Feb. 10. Lactose 9 gm. Urine positive for sugar.

Feb. 13. Lactose 7.5 gm. Urine negative for sugar. Tolerance continues within normal limits after a period of hepatic congestion lasting about three weeks.

April. During this month the functional activity of the liver as estimated by the phenoltetrachlorphthalein output in the fæces continued slightly below normal, it being 30 and 40 per cent (Dr. Whipple).

Autopsy.—After a period of six months the liver showed typical passive congestion with central atrophy and fatty degeneration.

In this animal the established normal tolerance before operation was 8.5 gm. lactose. Two days after the operation (cf. protocol) the animal was given 8 gm. lactose without excreting sugar. About three weeks after the operation and after a series of tappings, 7.5 gm. lactose (0.5 gm. below the normal tolerance) were fed without causing the appearance of sugar in the urine. It would appear, therefore, that in this animal the presence of chronic passive congestion of the liver was not associated with a reduction in the lactose tolerance.

CONCLUSIONS.

1. There is experimental evidence to show that in the intestinal tract of dogs lactose is split into its constituent molecules—dextrose and galactose—and that after feeding lactose to dogs, galactose is excreted in the urine.

2. Studies by various workers show that when lactose is split, the liver can form glycogen from galactose, but to a more limited extent and with greater difficulty than from the other monosaccharides.

3. The experiments cited show that it is more accurate to determine the tolerance of an animal before producing a liver injury than to accept arbitrary standards of normal tolerance, expressed either in total number of grams or in grams per kilogram of body weight.

4. Whereas the normal tolerance of dogs for lactose expressed in grams per kilogram of body weight is fairly constant, the total number of grams tolerated by different animals shows wide variations.

5. Eck fistula dogs show a reduced tolerance for lactose, which, however, may result from flooding of the systemic circulation with sugar rather than from liver injury.

6. In susceptible animals, central necrosis produced by chloroform poisoning results in the reduction of the lactose tolerance by 50 per cent or more.

7. In one animal with chronic passive congestion of the liver, no reduction in the lactose tolerance could be demonstrated.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

April 17, 1913.

On the Importance of Bacteriemia in the Diagnosis of Sinus Thrombosis of Otitic Origin. A Clinical and Bacteriological Study. E. LIBMAN, M. D., New York.

A brief abstract follows:

In the course of bacteriological studies of the blood (now numbering over 4700) of infections of various kinds, observations were made by us in cases of otitic infection which we believe to be of great importance from a diagnostic and therapeutic standpoint. The first publication of our results was made in the form of a discussion before the American Otological Society in June, 1906. Further observations made by Dr. Celler and the writer were reported at the meeting of the Association of American Physicians in 1909, and an exhaustive account of our results was presented last year before the International Otological Congress.

Dr. Celler and the writer studied 277 cases of otitis media and found that streptococci were present alone or with other organisms in 189 cases (81.46 per cent); *Streptococcus mucosus* occurred 20 times (10.3 per cent), and the pneumococcus 19 times (8.2 per cent). The organisms next most commonly found were the staphylococcus, *Bacillus pyocyaneus* and *Bacillus proteus*. Mixed infections were not uncommon. Although the pneumococcus is found in a comparatively large number of cases of otitis media, there are but few undoubted records of sinus thrombosis due to this organism. Until the time of reading this paper we had seen no case of sinus thrombosis surely due to the pneumococcus, but since then we have met one case with an atypical pneumococcus in the blood.

We have made blood cultures in 149 cases of otitis media and mastoid disease uncomplicated by sinus thrombosis and meningitis. Some were complicated by epidural and brain abscess. In all these cases the blood cultures were negative.

Our method consists in withdrawing ten to twenty-five cubic centimeters of blood from a vein (usually from an arm) and incubating this in a number of media, which are observed for five days. In children, and particularly infants, we are often compelled to use smaller amounts. Our studies in infants and in children under the age of six years is not extensive enough to warrant deductions. A couple of experiences make us believe that bacteriemia in children can arise more easily than in adults from uncomplicated otitis media or mastoid disease.

Anærobic methods were used occasionally. The method introduced by Duel and Wright, of New York, was also tried and gave no different results from our own method. Microscopical studies of the blood were made by Drs. Fried and Sophian, but the results are not sufficient to warrant advising the method.

Our positive results in blood cultures in cases of otitis media were obtained only in those complicated by meningitis or sinus thrombosis (including bulb thrombosis). There were six streptococcic meningeal infections; bacteriemia occurred in two. In three cases of pneumococcus meningitis the organism was found in the blood in one. In eight cases of meningitis due to *Streptococcus mucosus*, the cocci were were found in the blood in six.

In 43 cases of sinus thrombosis we obtained positive results in 34 (80 per cent); streptococci in 30 (90 per cent); *Streptococcus mucosus* in 3 (8.8 per cent); *Bacillus proteus*, once. We believe that nearly all cases of sinus thrombosis (except the aseptic type) are accompanied by bacteriemia at some time or other.

The possible causes of negative results in blood cultures of cases of sinus thrombosis are the following:

1. The organisms may be so few in number that none are obtained in the amount of blood used.

2. Anærobic organisms may be missed by not making use of a proper technique.

3. Cultures may be made before the organisms are present in the blood.

4. The cultures may be made after there are no more bacteria discharged from the local focus. This may be due to two reasons:

a. Organization.

b. The thrombus may break down, but instead of separate bacteria, pieces may enter the circulation and cause metastatic infections. Or if individual bacteria are also thrown into the circulation, they may be killed off, while those in the bits of thrombus are protected from the bactericidal power of the blood. In either event, one would have a case of metastatic infection (pyemia) without bacteriemia.

5. The bacteriemia may be intermittent.

6. The bactericidal power of the blood of the patient may be normally so marked or develop to such an extent that the bacteria are very rapidly killed off.

7. The end or ends of the clot may be bacteria-free even though the central part is infected.

8. The thrombus may be infective, but it may close the vessel in such a fashion that no bacteria are carried into the circulation.

9. The thrombus may have originally been bacteria-free or have become so.

As a result of our earlier studies, we claimed that cases in which streptococci are found in the blood after the mastoid has been operated upon (and in which clinical symptoms persist) are cases of sinus thrombosis. One must exclude all other possible primary foci. According to our late studies even those cases which before operation showed a bacteriemia, and in which other causes for the bacteriemia and meningitis could be excluded, proved to be cases of sinus thrombosis.

While there is a certain amount of evidence in the literature that a general infection can occasionally occur from the middle ear without sinus thrombosis being present, and while some of the literature on experimental investigations (much of which must be accepted with reserve) points the same

way, it is best that in any given case in which organisms are found, that the surgeon take for granted that the sinus is involved. He can then deal with the case according to the clinical condition of the patient at the time that the report is made. We recently had a case under observation in which we obtained a positive blood culture from the patient, but the symptoms were so mild that we desisted from advising operation. The temperature persisted for several days and the patient made a complete recovery. While this case may have been one in which spontaneous organization of a thrombus occurred (since spontaneous organization is not as uncommon as is generally believed), it is also possible that it is one of the exceptional cases in which a general infection occurred without a thrombus being present.

When present, the bacteria were usually found by means of blood culture, within twenty-four hours after the blood was obtained. The number of bacteria varied from one in several cubic centimeters of blood up to two hundred and forty-five per cubic centimeter of blood. They usually disappeared very promptly after operation upon the sinus and ligation of the jugular vein (sometimes in one or two hours). In the few cases in which they persisted in the blood, notwithstanding ligation of the jugular vein, there was usually found an extension of the thrombus to the other side or involvement of the bulb or an acute (ulcerative) endocarditis (this occurred in only one case), or a meningitis or a thrombosis of the jugular vein below the point of ligation.

The most valuable field for the blood culture studies has been in the cases in the border line between otitis and other diseases. In the publication made in the Transactions of the International Otological Congress for 1912 will be found a complete description of all cases in which blood cultures were found positive, and a study of these will show how remarkably valuable these investigations have been in clearing up doubtful cases.

The negative blood cultures also have a value. Absence of bacteria from the blood in a doubtful case would make one careful not to explore for a thrombus until the possibility of an intercurrent disease had been excluded or until symptoms had become so severe as to justify an exploratory procedure. If blood cultures should be negative in a given case and the symptoms persist, whether there is present a sinus thrombosis or not, acute (ulcerative) endocarditis can be excluded. In such cases it is advisable to take two cultures. A negative blood culture is also useful to prove that the general infection has been stopped, after ligation of the jugular vein has been performed.

As stated above, it is important to exclude all other possible primary sources of infection. There is not sufficient time to discuss all these; common ones are the following: Infections arising in the veins, lungs, bones, gall-bladder, appendix, kidneys, intestines, and male and female genito-urinary tracts. A number of forms of infection are particularly important to keep in mind, because they come into play so often in connection with cases of otitic infection. They are tonsillar infections, acute (ulcerative) endocarditis, accessory sinus infections, nasal infections, scarlet fever, typhoid fever, pneumonia and erysipelas. Accessory sinus infections seem to cause a general infection only when they are very severe. In scarlet fever there seems always to be a primary focus which is the point of origin of the streptococcemia. Fulminating cases of scarlet fever show no bacteriemia. In erysipelas, streptococcemia is very rare except in fatal or complicated cases.

When our paper was published in 1909, there was a certain amount of opposition to our views, particularly by Drs. Duel and Wright, of New York, who found general infection quite frequent in uncomplicated cases of otitis media and mastoiditis. A recent report by Page, from the same institution, gives results that entirely confirm our own. Similar results have also been found in the New York Eye and Ear Infirmary by Dr. Dixon and Dr. Hays.

DISCUSSION.

DR. H. O. REIK: As an otologist I believe I agree with Dr. Libman in practically all of his conclusions. To the otologist the value of the method will lie in the amount of aid and assistance it affords in making an early diagnosis of sinus thrombosis. In the past we have had to rely for diagnosis mainly upon the characteristic fluctuations of temperature noted in this disease, but the delay incident to such observations causes loss of much valuable time and, perhaps, of many lives that might be saved by earlier surgical intervention. Six years ago, during the Congress of Physicians and Surgeons, I read a paper before the American Otological Society presenting a résumé of the cases of lateral sinus thrombosis reported by members in the Transactions of that association from the time it was organized, and there were some striking features bearing upon the importance of early diagnosis and proper methods of operation.

Dr. Libman has remarked that sinus thrombosis may get well without operation. There is no question about that, for there are a number of cases reported where the diagnosis would appear to be almost certain and yet the patients got well without operation upon the vessel. Nevertheless, in spite of these clinical records and of the experimental evidence of organization, recanalization and so forth, it is equally true that lateral sinus thrombosis, if left untreated or if treated without surgical assistance, has a very high mortality, almost 100 per cent. Even with direct operation upon the sinus, the mortality is high, about 60 per cent, when the sinus is opened and the thrombus attacked without preliminary ligation of the internal jugular vein. If the vein be first ligated and the diseased portion of the sinus then treated, the mortality drops to 25 per cent, or thereabouts. I mention these findings because of what Dr. Libman said about inspection of the supposedly diseased sinus as a means of diagnosis. I want to emphasize the fact that the otologist cannot by this means, except occasionally, make a positive diagnosis and that he can never say there is not a thrombus present. There may be a parietal or even a complete thrombus without visible signs on the external surface of the vessel. Furthermore, in

any method of palpation of the sinus or of puncturing that vessel to secure material for examination you take additional risk of disseminating infection. If lateral sinus thrombosis is suspected the sinus may be exposed and prepared for incision, but should not be touched until after ligation of the jugular; having placed a barrier in the way of extension, by tying off the vein, one may deal with the sinus without fear of inducing further trouble.

However, looking into the future, I would say that if we are to save a larger proportion of these infections of the lateral sinus we must endeavor to recognize the beginning of the attack upon the sinus by the otitic disease. These cases practically all begin with a phlebitis of the sinus wall, a clot begins to form on the inner wall of the vessel, becomes infected, and, with breaking down, causes dissemination of poison through the vascular system. It must be made possible for us to recognize and diagnose the stage of inflammation of the vessel wall, the phlebitis, that we may operate before the thrombus is organized, or, at least, before it becomes a focus of infection.

Now, Dr. Libman made an exception to some of his conclusions regarding thrombosis of the sinus in children and I want to say that possibly the reasons for this exception are more apparent than real. We must not forget that this affection in children has probably been often overlooked, because the infection is prone to occur in a different position from that of the adult. McKernon has shown that in young children the infection happens frequently, but that it occurs in the portion called the bulb of the jugular vein rather than in the sigmoid curve, as is general in adults. That is, in adults the disease attacks the upper part of the sinus from the mastoid cells, while in the child it reaches the vessel through the floor of the tympanic cavity.

Dr. Libman: I have seen about 30 cases of pylephlebitis. In only one of them did I succeed in getting a positive blood culture; it is interesting to note that in that case the foramen ovale was open. The fact that bacteria are not generally found in the blood current in pylephlebitis is a very interesting one, and I have made the same observation that Dr. Thayer has made, that one can use this fact in helping to establish the diagnosis in certain cases in which one is in doubt as to whether there is an acute or subacute bacterial endocarditis or a suppurative pylephlebitis.

The bacteria are probably not found in the blood in the cases of pylephlebitis, because the pieces which are dislodged from the portal vein are caught in the liver and produce local infections there. It is, furthermore, of interest to note that whenever one gets an infection in any part of the body in which there is an abundance of carbohydrate, one is not apt to see a general infection develop. This not only holds true of infections of the liver, but is particularly of interest in connection with infections of the lactating breast. I cannot remember having seen a case of general infection arising from suppuration in the lactating breast, no matter how severe the clinical picture was. It must be an unusual occurrence. I might also express here my surprise at the comparative infrequency of general infections in diabetics, notwithstanding the frequency of local infections in them.

I have stated these facts because they have impressed themselves upon me in the course of my studies. How far they will be affected by further experience I do not know.

There is one point I would like to bring out, and that is concerning the question about ligating the jugular vein before operating upon the sinus. If one is at all sure that a sinus thrombosis is present, it is better to ligate. In one case which I have seen, in which the jugular vein was not ligated before the sinus was operated upon, there was a marked increase in the number of bacteria in the blood following the operative procedure. This patient developed an acute bacterial endocarditis (malignant endocarditis). Of course, one cannot claim that the endocarditis would not have developed anyhow, but it certainly would have been better to have avoided throwing more bacteria into the blood current than had been present before. Every once in a while we see a case on the operating table that goes into collapse, and in some of these cases I believe the collapse is due to dislodging of bits of thrombus from the sinus. If the operator is not certain that a sinus thrombosis is present, he might explore the sinus, and as soon as he sees evidence that a thrombus is present, perform the jugular operation and then go back and attack the sinus.

It is not to be forgotten that there are some reports in the literature of cases of spontaneous recovery from sinus thrombosis without operation. A number of observers have described cases of organization and canalization of thrombi in the lateral sinus in cases in which no operation whatsoever was done upon the sinus. My general impression is that this is more apt to occur in children than in adults.

April 21, 1913.

Exhibition of a Case of Chorio-epithelioma. Dr. J. Whitridge Williams.

DISCUSSION.

Dr. Cullen: Last year I reported before the Society a case of hydatidiform mole with bilateral multiple corpora lutea cysts.

The patient (Mrs. H. B. S.), was 20 years old. Her last menstrual period had occurred on Nov. 19, 1911. On Dec. 15 she noticed a small drop of blood. On Feb. 3 she had a fall and went to bed. On the night of the fall she had a chill and commenced having pains in her abdomen. On Feb. 6th discharge of blood and water was noted and her family physician, Dr. George Hocking, then examined her and said she was threatened with a miscarriage. From Feb. 6th up to March 9th, when I saw her, there had been a discharge of blood each day. On Feb. 28th there was some swelling of the feet and the following day her face began to swell.

On March 10th the uterus was dilated and numerous hydatid cysts came away. On March 23d the patient was doing remarkably well, but masses were still present posterior to the uterus, just above the cul-de-sac.

On opening the abdomen we found bilateral multilocular ovarian cysts, each about 8 x 5 x 4 cm. They lay beneath the uterus, which was twice its natural size. On account of the age of the patient I hesitated to remove both ovaries completely; I therefore resected them, saving a small portion at the hilum of each ovary. When the operation was completed the ovary on either side of the uterus was about half its natural size. Each of the multilocular cysts contained clear fluid, and was evidently a corpora lutea cyst.

A month ago I learned from Dr. Hocking that this patient had become pregnant, but a few weeks before term she had had a fall and consequently the child was born dead.

This case demonstrates what we can sometimes do by conservative operations. There was evidently sufficient ovary left on either side to provide for a subsequent pregnancy.

Histological examination of the cysts showed that they were all corpora lutea cysts.

The possible coexistence of these multilocular cysts with hydatid mole should always be thought of, as in some instances the thickening on either side of the uterus has led the surgeon to believe that the uterus contained a malignant growth and that the lateral thickening was due to an extension of the supposed chorio-epithelioma to the broad ligaments.

Three years ago we had a very interesting inoperable case of chorio-epithelioma in Ward H. (Gyn. No. 18034; Path. No. 16776). Each Bartholin's gland was over 1 cm. in diameter and on being squeezed the contents escaped as a small ribbon similar to that from a tube of tooth paste. This tissue on microscopic examination proved to consist of typical chorio-epithelioma. Pathologists experience great difficulty in differentiating histologically between simple hydatid mole and chorio-epithelioma. As a rule the diagnosis can be definitely made only when a portion of the uterine wall has been invaded or when metastases exist. The clinical picture is of the greatest importance in determining whether or no malignancy exists.

Dr. Williams was particularly fortunate in his diagnosis of this condition from scrapings and in the substantiation of his opinion by the findings in the uterus after its removal.

Plague. DR. RICHARD P. STRONG.

DISCUSSION.

DR. CHAS. W. YOUNG: *Mr. Chairman:* I don't suppose this meeting realizes the great amount of information that Dr. Strong has brought to us this evening. Dr. Strong, by his investigations in Manchuria, has added very much to our knowledge of the pneumonic plague. While others were referring to their past work, he was out in the field doing something, and in the International Plague Conference Dr. Strong was able to bring evidence as to what he had found out. He has not discussed his previous and very interesting work on immunity in *bubonic* plague. There is a point about the mask of which he has spoken. It was perhaps useful in Mukden, but at Harbin the temperature reached 35 or 40 degrees below zero. You can realize that when one went out in such a temperature the mask became covered with a coating of ice and the air did not go through the mask, so there was little protection from it. If goggles were used it was extremely difficult to see on account of the condensation on the lenses. In examining patients in the open air I believe that the goggles can be dispensed with. There is always a bacteræmia in pneumonic plague. In five cases cultures were positive, four of them in living patients and one in a cadaver of a patient recently dead so there is a bacteremia at least in the later stages of the disease.

Dr. Strong has spoken of autopsies he performed. These twenty-five necropsies are more than all the previous discriptions of pneumonic plague had been based on. He performed the first autopsies that have ever been performed in China with official cognizance.

May 19, 1913.

Multiple Congenital Osteochondromata, etc. DR. T. R. BOGGS.

DISCUSSION.

DR. BLOODGOOD: The case reported and illustrated by Dr. Boggs is one of great interest and extreme rarity.

I have been interested in lesions of bone for many years, and while I have seen many examples of single bone lesions, multiple lesions are very infrequent.

There is no doubt that in Dr. Boggs' case there are multiple exostoses. These are visible and palpable without the aid of the X-rays, but, in addition, there seem to be changes in the marrow cavity of some of the bones. These changes are most marked in the tibia, humerus and upper end of the femur. Unfortunately in this case there has been no opportunity as yet, either by operation or autopsy, for examination of either the exostoses or of the bone marrow. In addition, this case shows other defects in the osseous system, especially bending of bone as shown in the radius, humerus and necks of the femora. Up to this time, in the literature I know of no case of multiple exostoses in which the bone marrow has been examined either at operation or autopsy. Dr. Boggs' patient also exhibits congenital defects in the nervous system and in the muscles. From my reading of the literature and limited experience, I am inclined to view this case as an example of congenital multiple exostoses. These exostoses may be bone, or cartilage, or both. The defect begins perhaps in early embryonic life and is in the development of the osseous system. We have as yet no proof that the bone changes depend upon any of the ductless glands, such as the thyroid or pituitary body. These patients at birth and in young childhood may exhibit no signs of the exostoses, but later in life, especially during puberty, growth in one or more of the exostoses may take place, giving rise to visible and palpable tumors with or without pressure symptoms.

Dr. Dunlop of Washington sent me X-ray studies of the father and three sons—all exhibiting multiple congenital exostoses, but none of these patients suffered from the bone lesion.

In a recent article by Paul Frangenheim (Beitr. z. klin. Chir., 1911, LXXIII, 226), read since I discussed Dr. Boggs' paper, I find that in an autopsy investigation in a case of multiple cartilage exostoses changes were also found in the marrow cavity—cartilage formations.

As a rule we have observed in diseases of bone similar pathological processes occurring in a single bone and in many bones. I was especially interested in this phase of the question in an investigation on benign bone cysts, giant-cell sarcoma and bone aneurysms (Transactions of the Amer. Surg. Asso., 1910; Annals of Surgery, August, 1910). I was able then to collect from the literature examples of cyst formation in the following diseases of the skeleton: Ostitis fibrosa (von Recklinghausen's disease), 12 cases; ostitis deformans (Paget's disease), 5 cases; osteomalacia, 6 cases; cysts in multiple enchondromas, 2 cases; in multiple sarcoma, 1 case; and in multiple bone lesions of mercurial poisoning, 1 case. In multiple myeloma I was unable to find any recorded case of cyst formation, nor in the cases of multiple carcinoma metastases to bone, nor in multiple exostoses of the congenital type. The full literature is given in my article.

Of all these lesions of the skeleton the enchondroma and exostosis are the only examples of bone defects of congenital origin. It is also interesting to note that in these two lesions no examples of malignant degeneration have been observed. We also do not know why in some cases of multiple congenital exostoses the tumors remain quiescent, in others they grow at different periods of life after puberty, giving rise to all grades of deformity and discomfort.

Dr. Boggs' patient is an example of the most exaggerated form of this condition. It would be very interesting to know, if we could be able to prevent the later development of these serious changes of a congenital lesion, which, as a rule, in early life gives rise to no discomfort or deformity.

There is no doubt that the development of bone depends upon a normal thyroid and pituitary gland, and we now know also that serious joint and osseous lesions may be produced by poisons, such as mercury, as well by toxins, such as from the intestinal tract. The presence of Bence-Jones bodies has not been found in these cases of multiple exostoses. It usually occurs in the multiple myeloma and now and then in metastatic carcinoma. Dr. Boggs, I think, has also reported an example of the latter.

I hope that Dr. Boggs will be able in his case to have an opportunity for careful investigation of the chemistry and histology of the bone lesion.

Dr. Boggs: In reply to Dr. Bloodgood's inquiry about autopsies I would say there have been some, but a very few. A few exostoses have shown cystic degeneration, but for the most part the descriptions of these tumors is like that of normal bone. I have found no reference to any changes in the marrow.

Report of Cases. Dr. T. S. Cullen.

DISCUSSION.

Dr. Bloodgood: The cases reported by Dr. Cullen and the one by Dr. Boggs bring out the interesting fact that we know very little of the etiological factors in most tumors, either benign or malignant. We are quite familiar with many congenital tumors—exostoses, lipomas, pigmented moles, nævi, fibromyxomas of nerve-sheaths, the basocellular epithelial tumors, and the embryoma in the region of the testes and the ovary. It is not at all difficult to explain the presence of these tumors by displacement of cells in embryonic life, but the factor or factors which lead later in life to growth, either benign or malignant, in these congenital "Anlagen" we have not ascertained as yet.

From a large experience investigators are beginning to feel that a single or continuous trauma, or some form of irritation, may be a factor which leads to later growth.

The same is true of certain inflammatory tumors. As a rule, after a wound or an inflammation, the inflammatory reaction is sufficient to accomplish the healing of the wound, or the resolution of the inflammation, but in rare instances the inflammatory reaction is far out of proportion to the irritant. We observe this in certain keloid tumors, in the so-called desmoid tumors of the abdominal wall, in fibro-spindle-cell tumor formations, in areas of skin the seat of acne, in the so-called fibromatosis or linitis plastica of the wall of the stomach about an ulcer, in certain cases of chronic appendicitis, where the inflammatory thickening of the appendix is unusual, in some large inflammatory tumors of the colon about small diverticula. Nor can we explain why the new formation in the benign congenital tumor, or in the inflammatory tumor, remains benign in spite of the increased growth in some cases, while in others, at various intervals, malignant degeneration takes place.

In the treatment of such cases the possibility of a malignant change must always be borne in mind. It is on account of this possibility that surgeons now advocate the complete removal of all such benign congenital tumors and apparently benign inflammatory tumors.

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